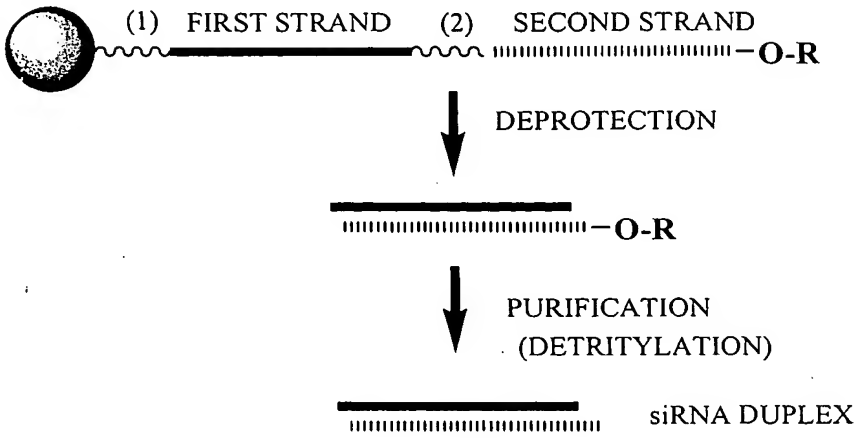
# *Figure 1*

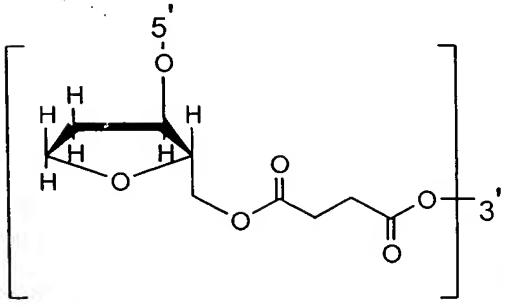



= SOLID SUPPORT

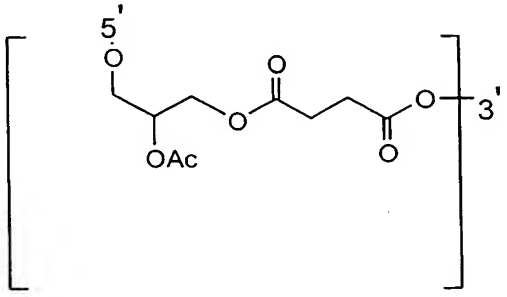
**R** = TERMINAL PROTECTING GROUP
FOR EXAMPLE:
DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

(2) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR INVERTED DEOXYABASIC SUCCINATE)

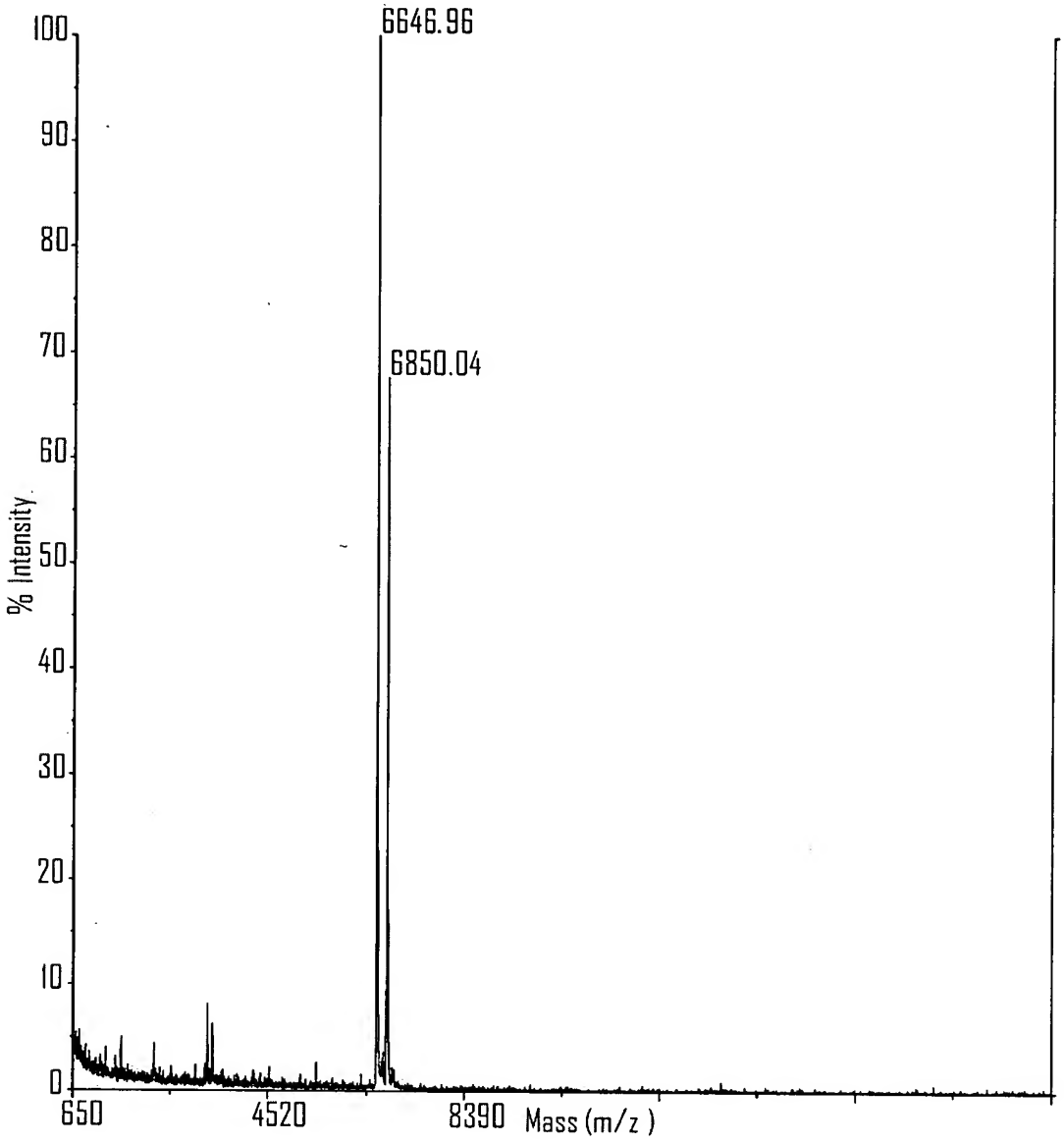



INVERTED DEOXYABASIC SUCCINATE LINKAGE




GLYCERYL SUCCINATE LINKAGE

# *Figure 2*


6646.96
6850.04
100
90
80
70
60
50
40
30
20
10
0
% Intensity
650
4520
8390
Mass (m/z)

# Figure 3

| | |
|---|---|
| 5'-CGUACGCGGAAUACUUCGATT (SEQ ID NO: 394)<br>3'-TTGCAUGCGCCUUAUGAAGCU (SEQ ID NO: 395) | T ½ = 15 seconds (control) |
| 5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396)<br>3'-TXGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 397 ) | T ½ = 138 min |
| 5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396)<br>3'-TDGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 398 ) | T ½ = 3.7 days |
| 5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396 )<br>3'-XTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 399 ) | T ½ = 72 minutes |
| 5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396)<br>3'-LTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 400) | T ½ = 40 days |
| 5'-B cAAccAcAAAAuAcAAcAATT B (SEQ ID NO: 396)<br>3'-tTGuuGGuGuuuuAuGuuGuu (SEQ ID NO: 401) | T ½ = 32 days |

G, A, U, C = Guanosine, Adenosine, Uridine, Cytidine
T = Thymidine
Lower Case = 2'-deoxy-2'-fluoro
S = phosphorothioate
B = inverted deoxyabasic
D = inverted Thymidine
X = 3'-deoxy Thymidine
t = L-thymidine
L = Glyceryl moiety

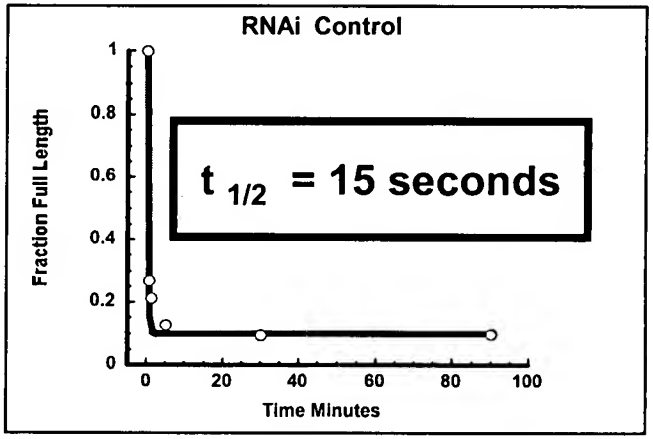


*Figure 4*

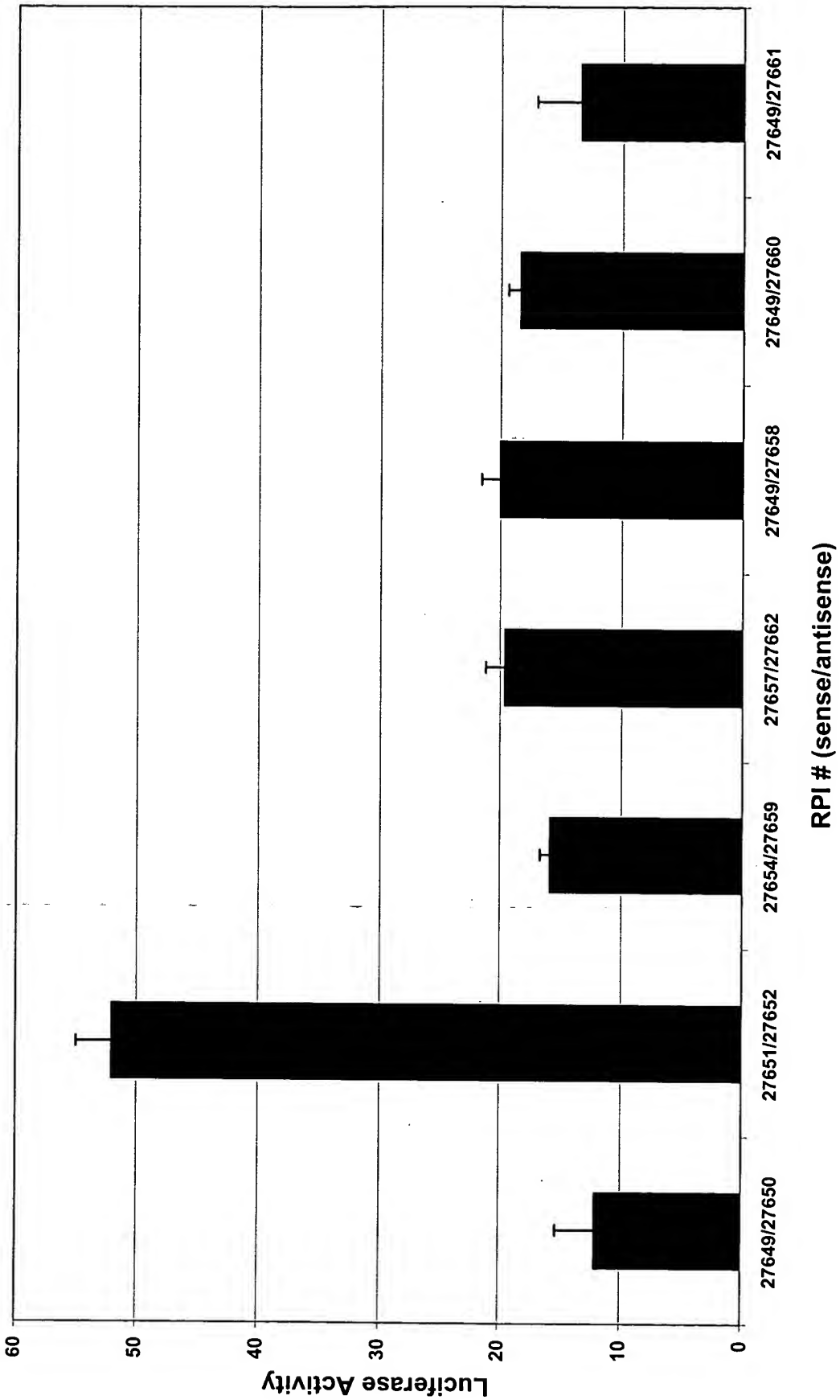

Luciferase Activity
60
50
40
30
20
10
0
27649/27650
27651/27652
27654/27659
27657/27662
27649/27658
27649/27660
27649/27661
RPI # (sense/antisense)

*Figure 5*

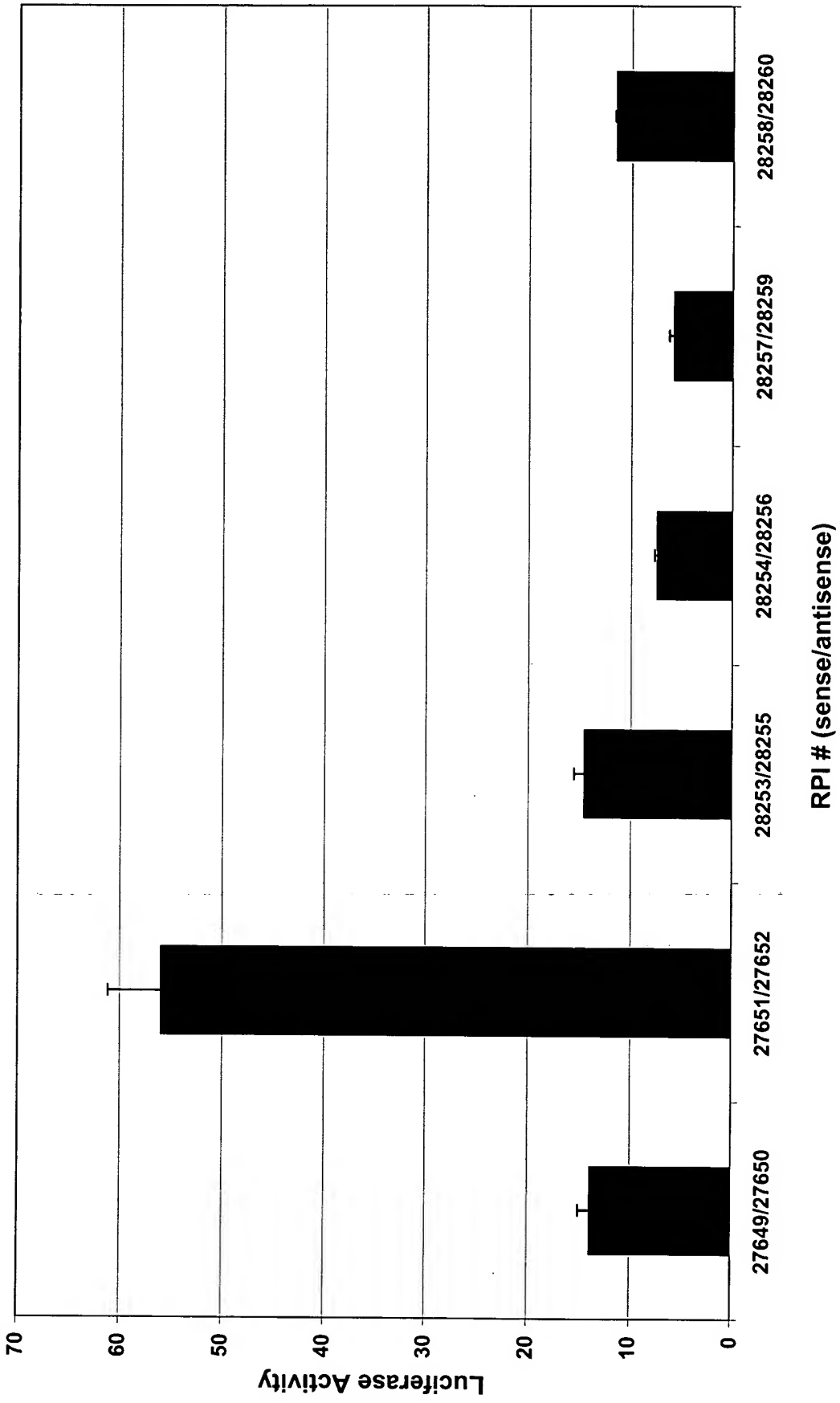

Luciferase Activity
70
60
50
40
30
20
10
0
27649/27650
27651/27652
28253/28255
28254/28256
28257/28259
28258/28260
RPI # (sense/antisense)

*Figure 6*

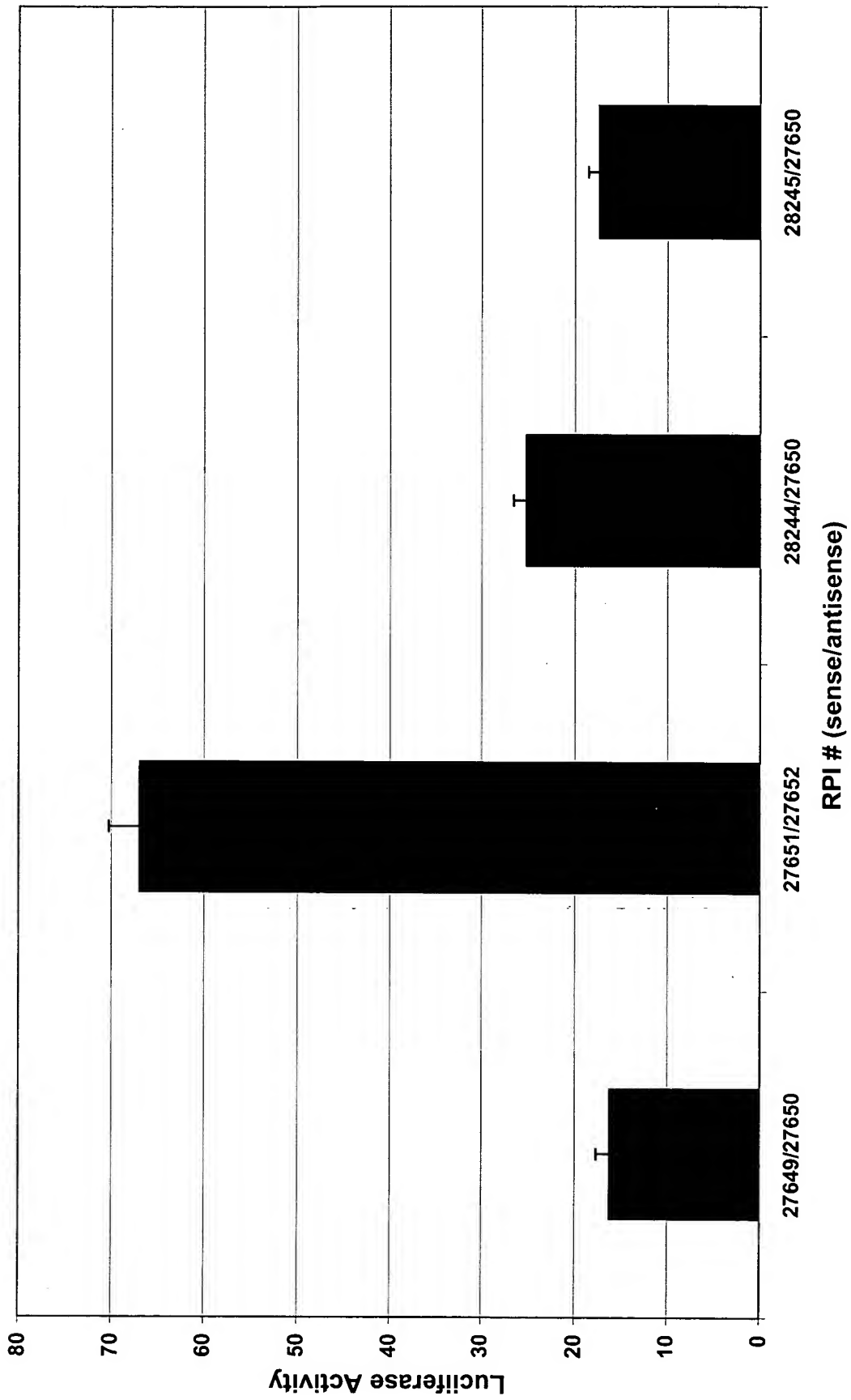

Luciferase Activity
0
10
20
30
40
50
60
70
80
27649/27650
27651/27652
28244/27650
28245/27650
RPI # (sense/antisense)

*Figure 7*

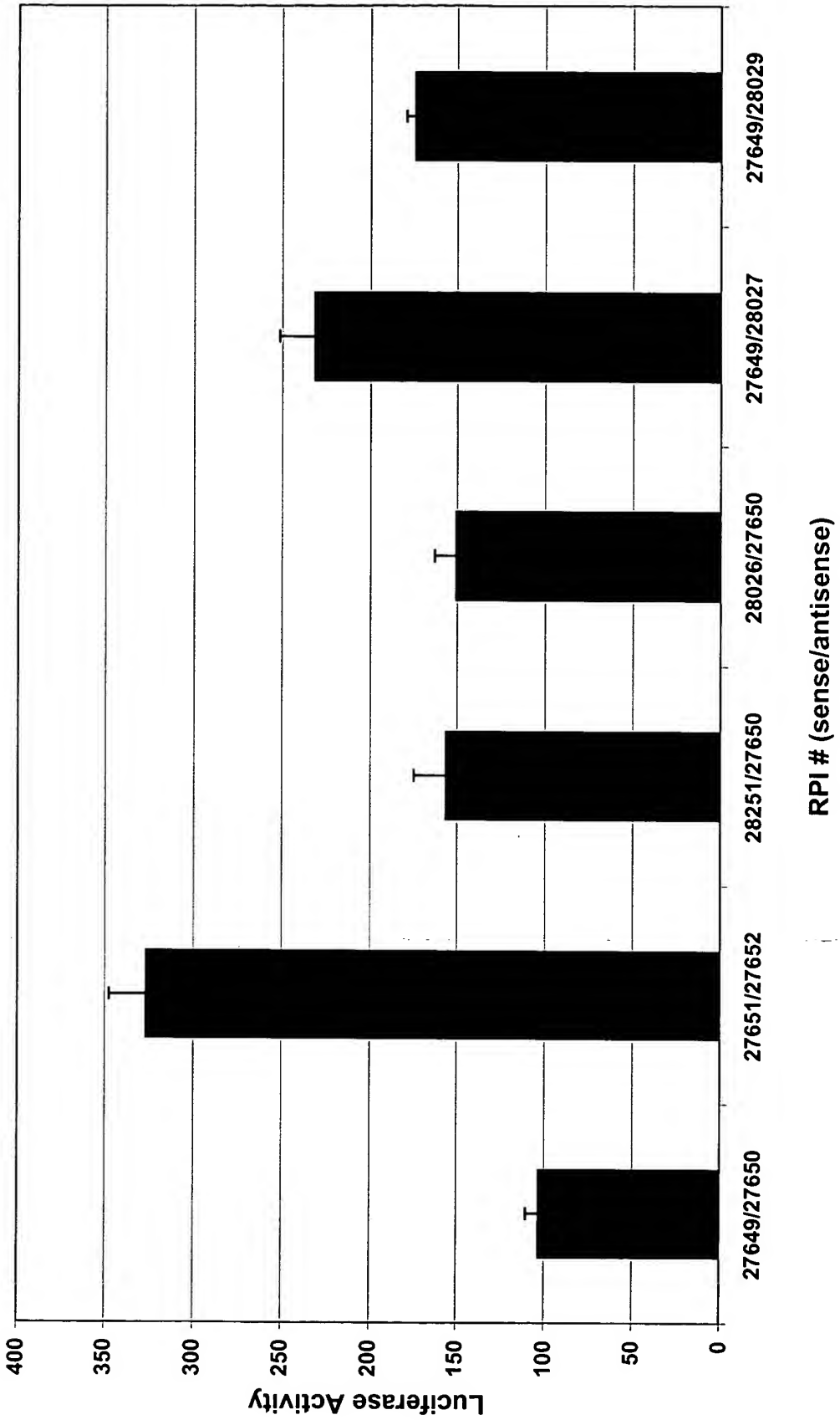

Luciferase Activity
400
350
300
250
200
150
100
50
0
27649/27650
27651/27652
28251/27650
28026/27650
27649/28027
27649/28029
RPI # (sense/antisense)

*Figure 8*

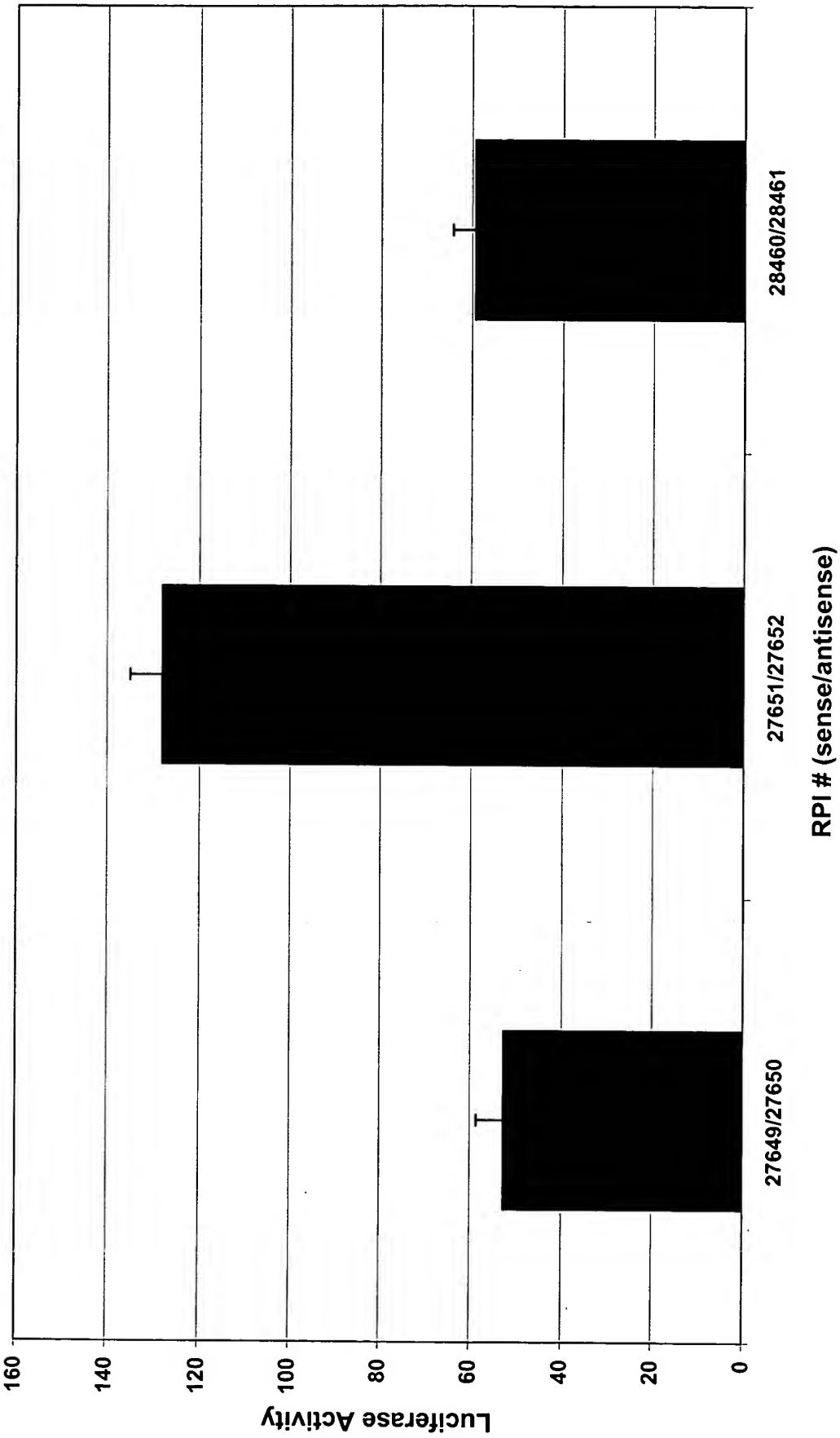

Luciferase Activity
160
140
120
100
80
60
40
20
0
27649/27650
27651/27652
28460/28461
RPI # (sense/antisense)

*Figure 9*

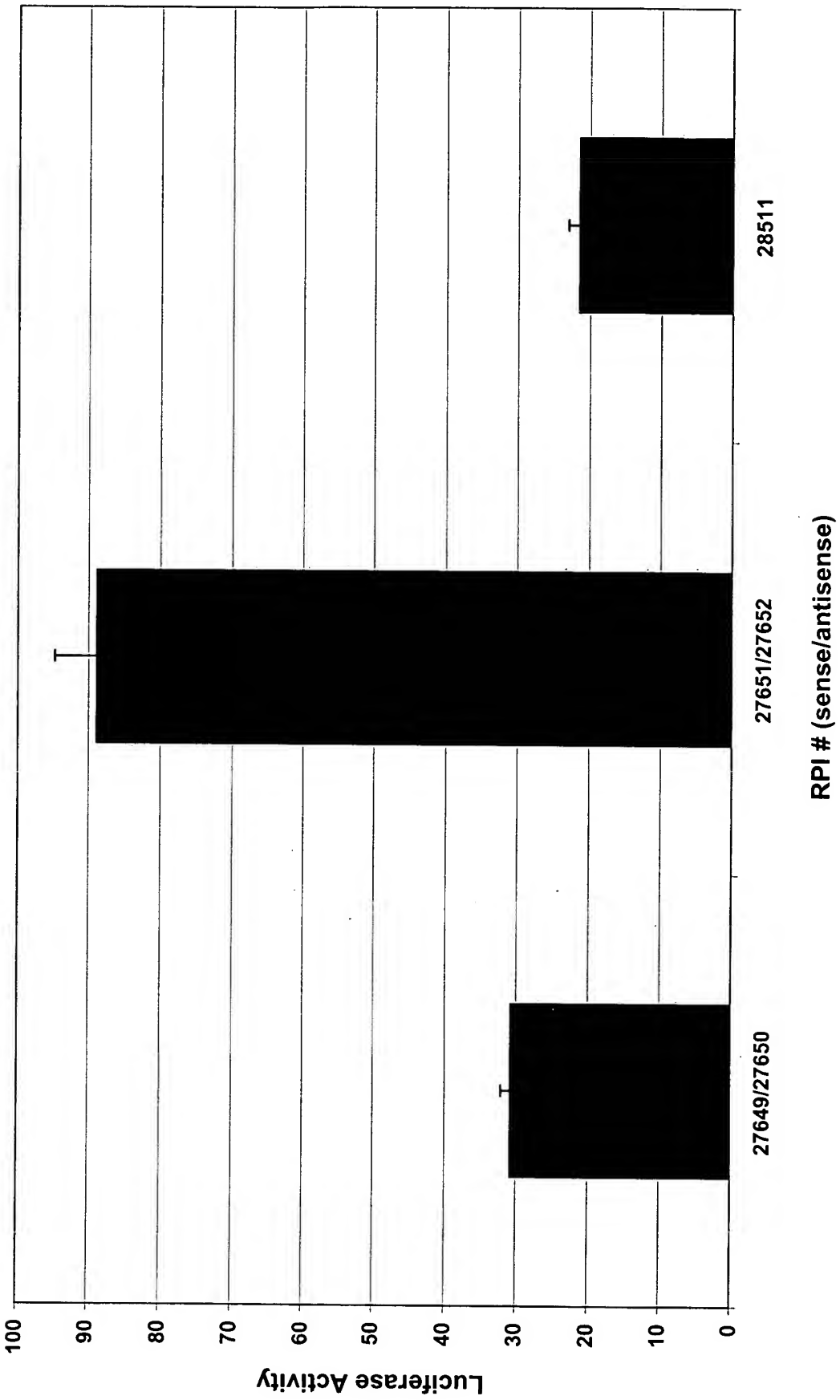

Luciferase Activity
100
90
80
70
60
50
40
30
20
10
0
27649/27650
27651/27652
28511
RPI # (sense/antisense)

Figure 10

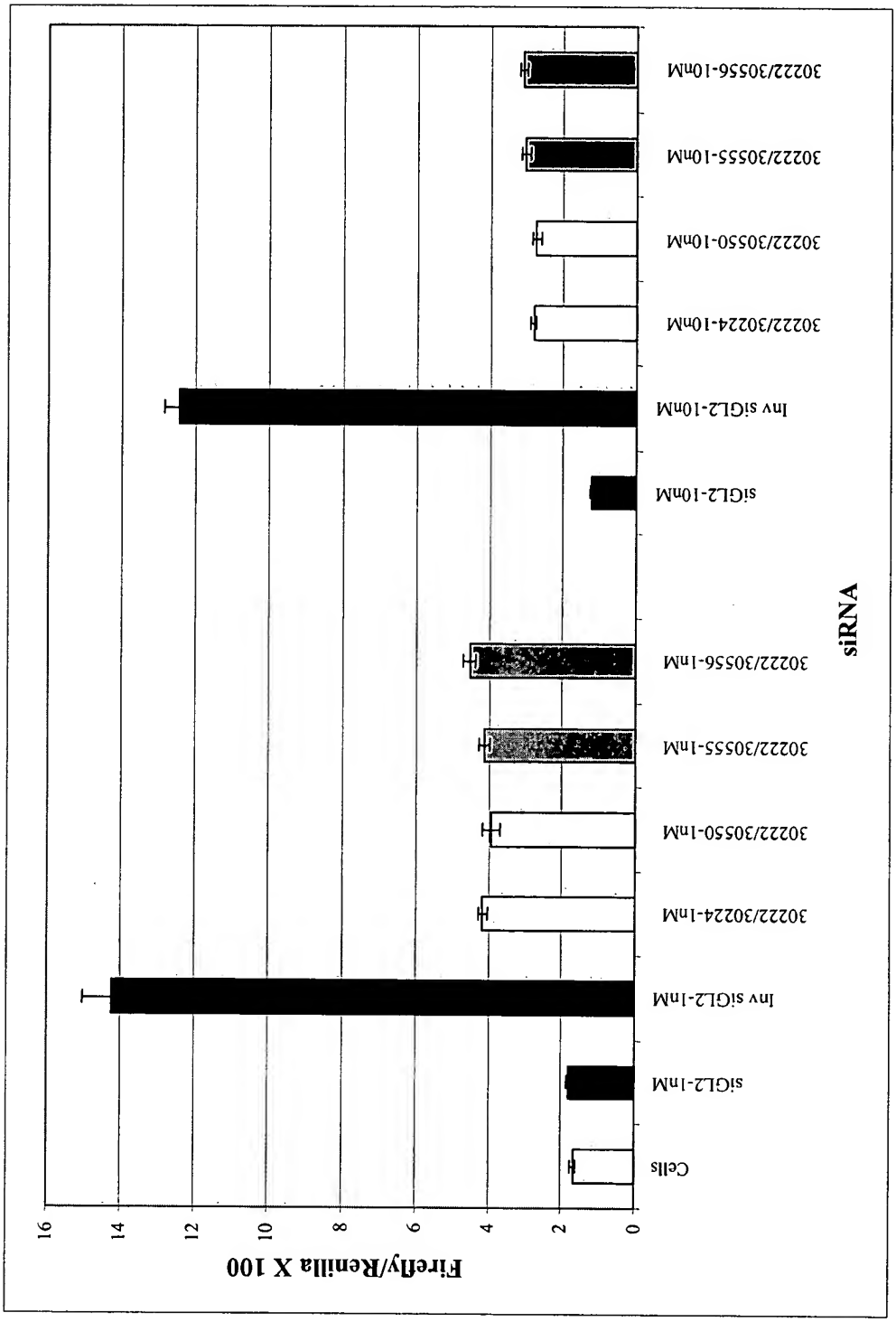

Cells
siGL2-1nM
Inv siGL2-1nM
30222/30224-1nM
30222/30550-1nM
30222/30555-1nM
30222/30556-1nM
siGL2-10nM
Inv siGL2-10nM
30222/30224-10nM
30222/30550-10nM
30222/30555-10nM
30222/30556-10nM
siRNA
Firefly/Renilla X 100
0
2
4
6
8
10
12
14
16

Figure 11

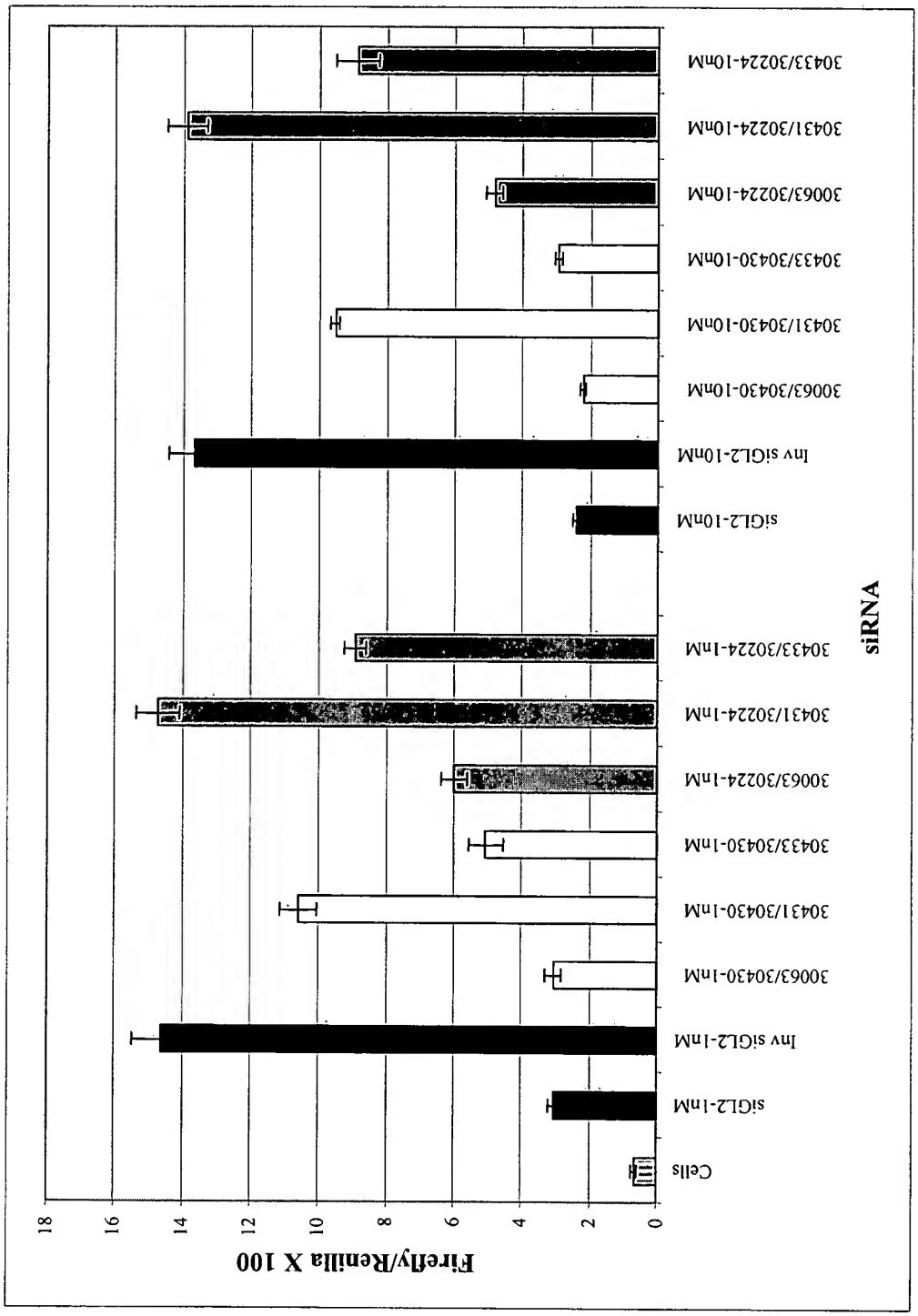

Firefly/Renilla X 100
0
2
4
6
8
10
12
14
16
18
siRNA
Cells
siGL2-1nM
Inv siGL2-1nM
3006/30430-1nM
30431/30430-1nM
30433/30430-1nM
3006/30224-1nM
30431/30224-1nM
30433/30224-1nM
siGL2-10nM
Inv siGL2-10nM
3006/30430-10nM
30431/30430-10nM
30433/30430-10nM
3006/30224-10nM
30431/30224-10nM
30433/30224-10nM

Figure 12

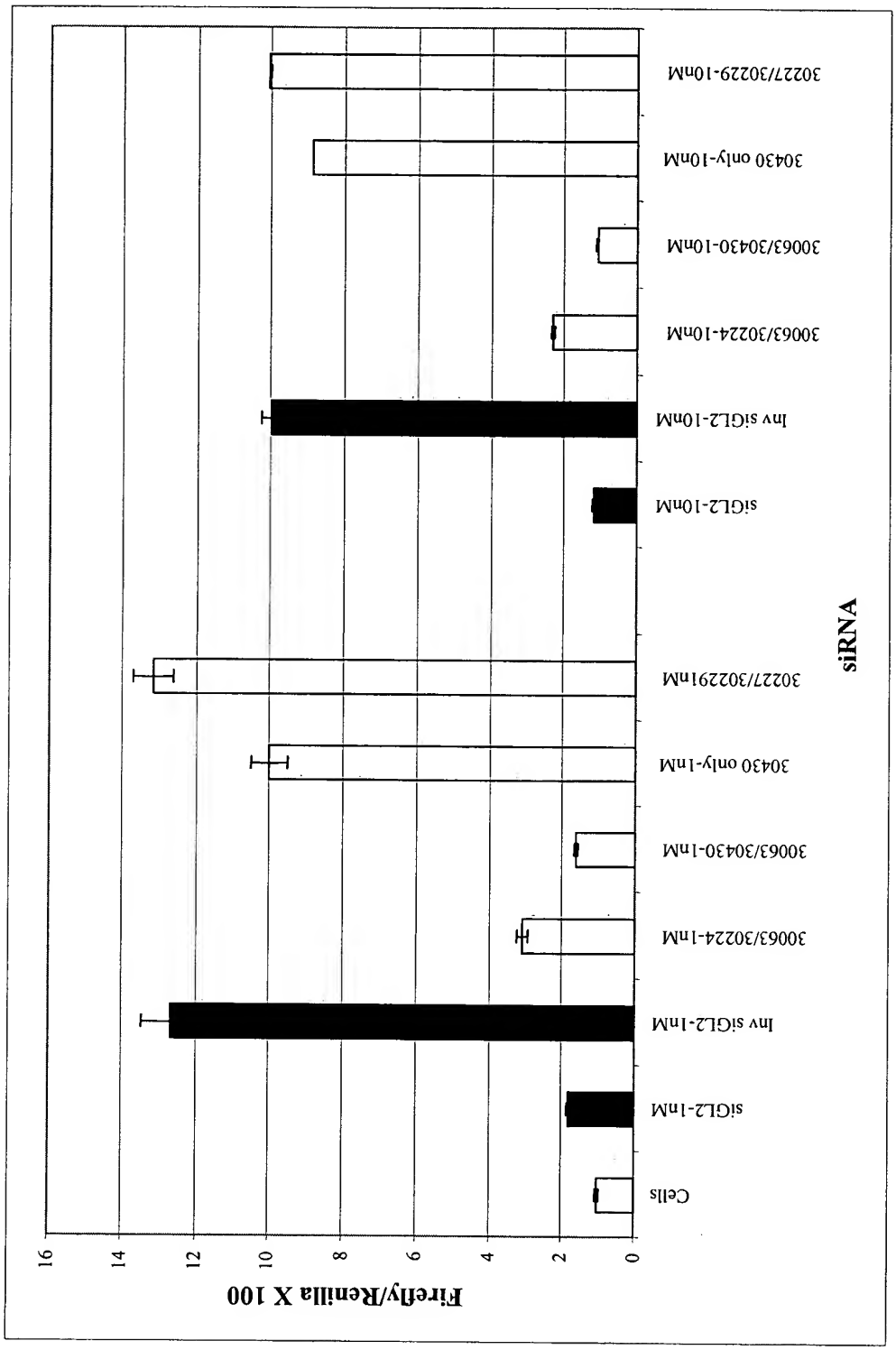

Firefly/Renilla X 100
0
2
4
6
8
10
12
14
16
siRNA
Cells
siGL2-1nM
Inv siGL2-1nM
30063/30224-1nM
30063/30430-1nM
30430 only-1nM
30227/30229-1nM
siGL2-10nM
Inv siGL2-10nM
30063/30224-10nM
30063/30430-10nM
30430 only-10nM
30227/30229-10nM

Figure 13

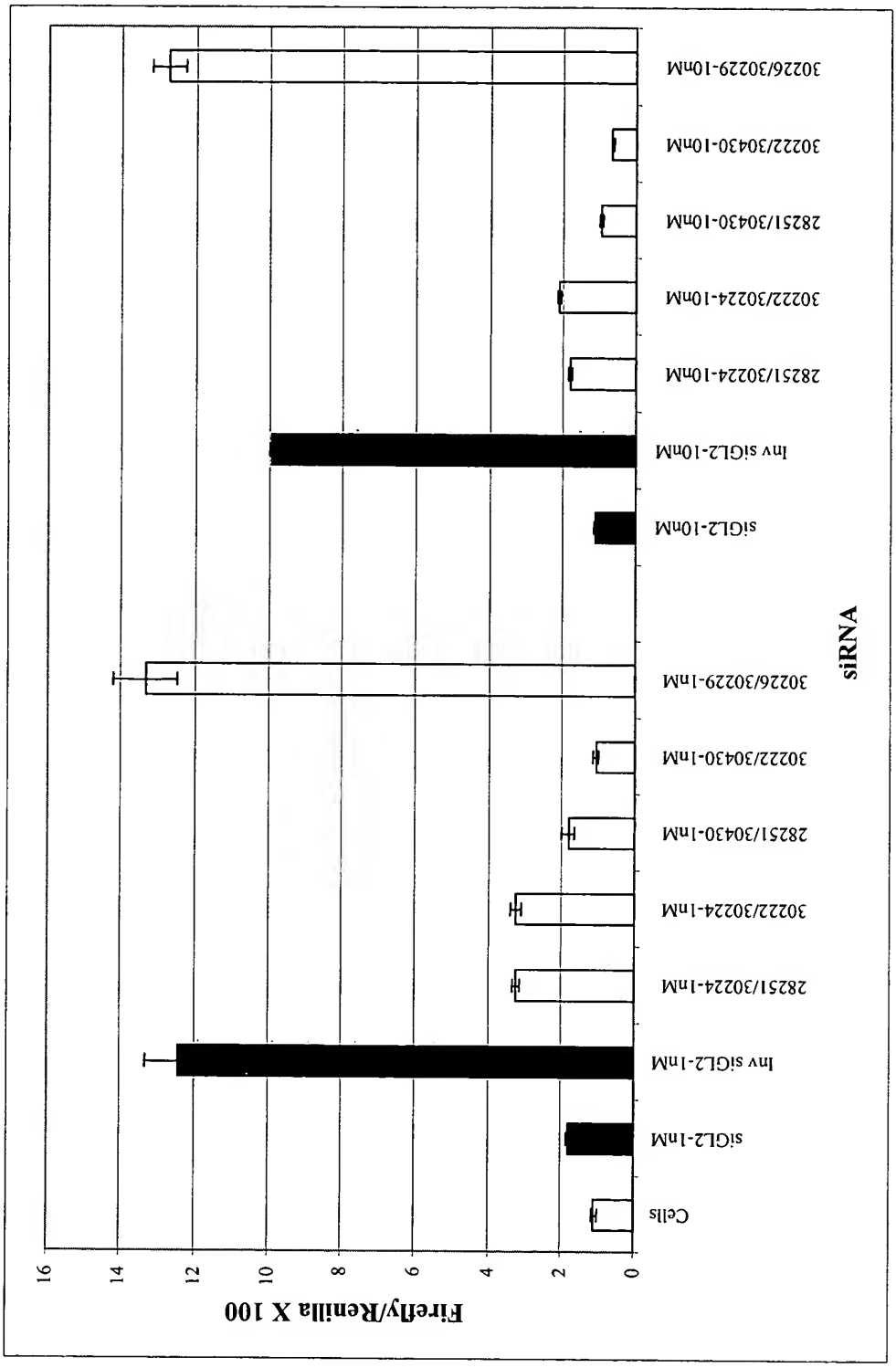

Firefly/Renilla X 100
0
2
4
6
8
10
12
14
16
siRNA
Cells
siGL2-1nM
Inv siGL2-1nM
28251/30224-1nM
30222/30224-1nM
28251/30430-1nM
30222/30430-1nM
30226/30229-1nM
siGL2-10nM
Inv siGL2-10nM
28251/30224-10nM
30222/30224-10nM
28251/30430-10nM
30222/30430-10nM
30226/30229-10nM

Figure 14

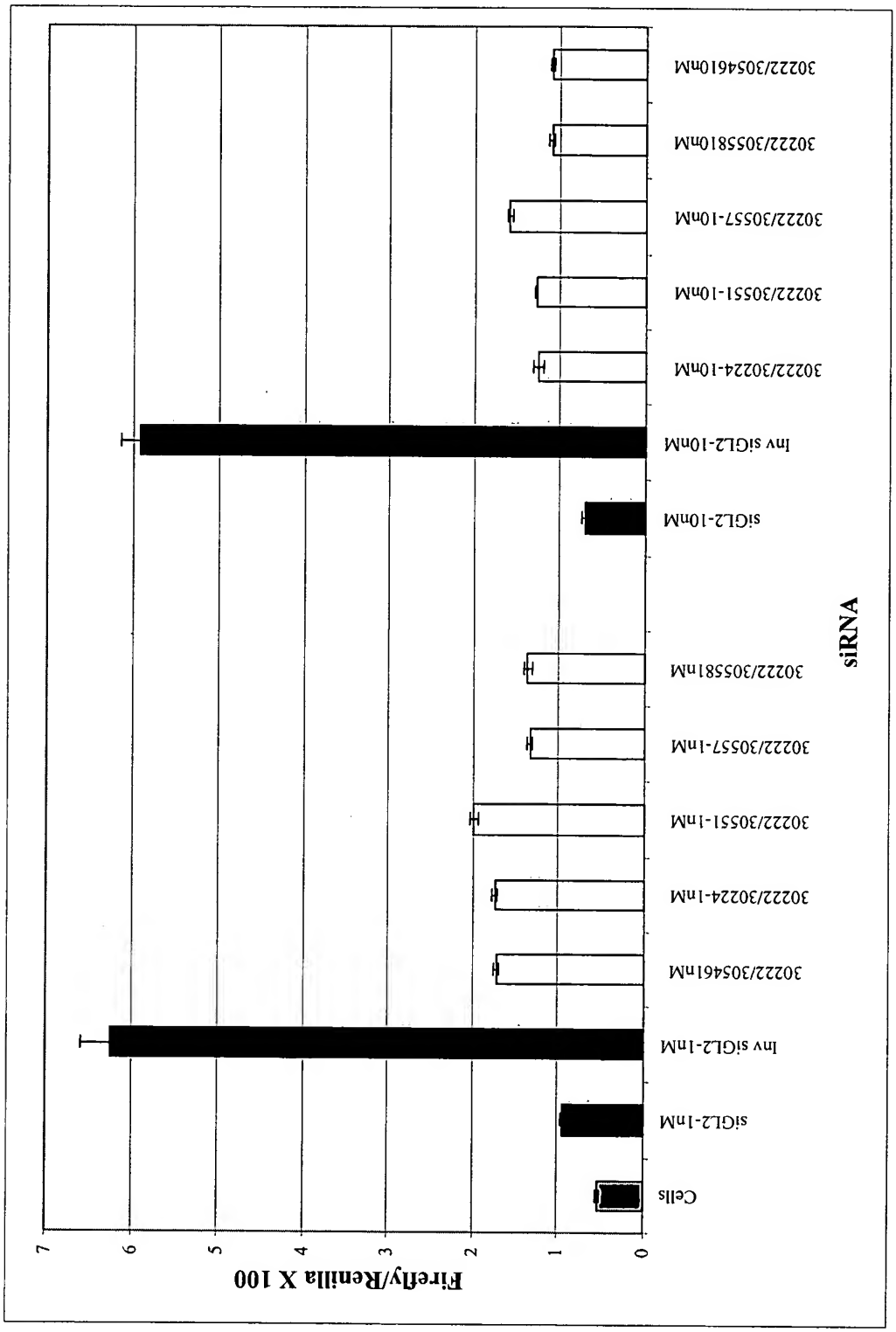
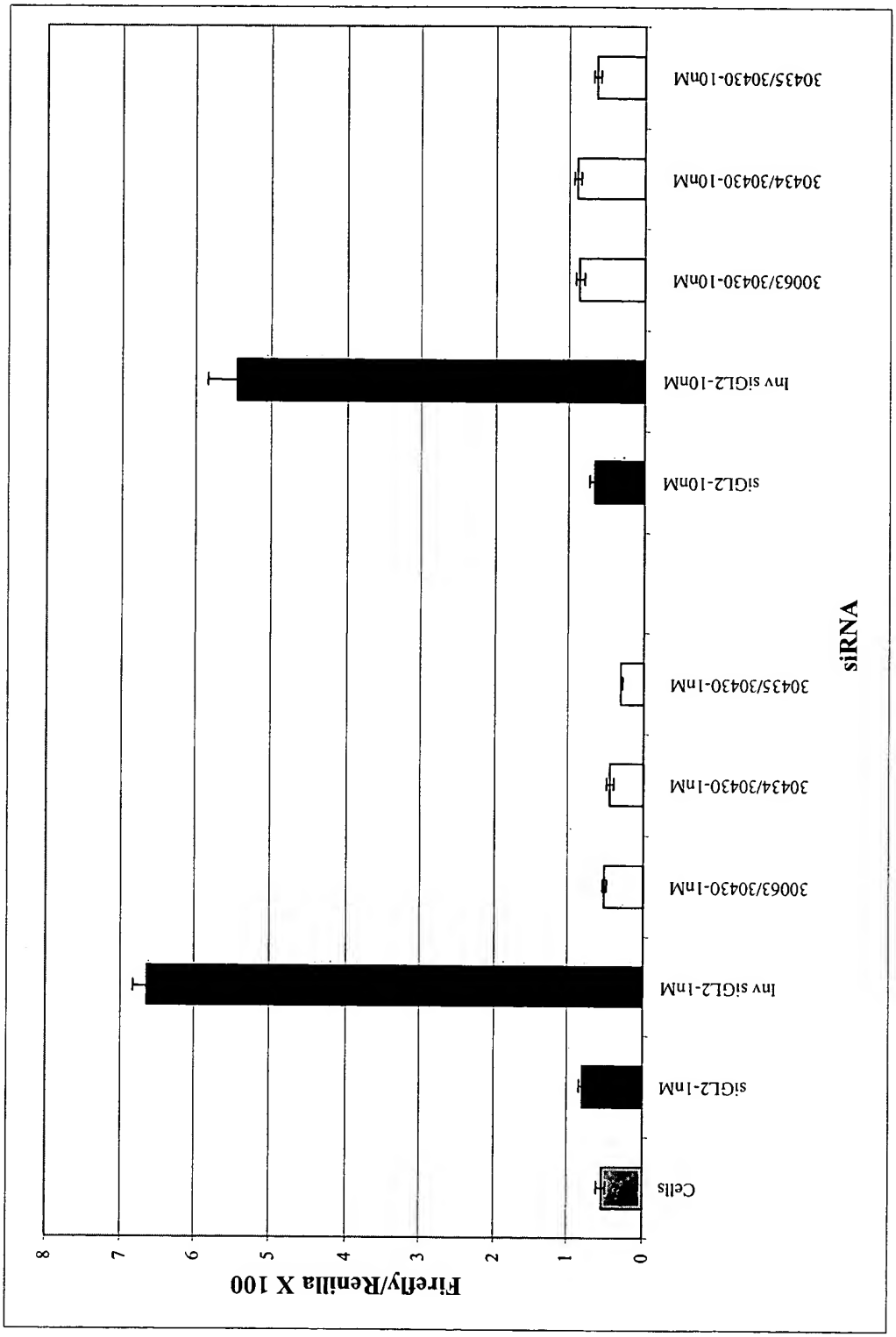

Firefly/Renilla X 100
0
1
2
3
4
5
6
7
siRNA
Cells
siGL2-1nM
Inv siGL2-1nM
30222/30546 1nM
30222/30224-1nM
30222/30551-1nM
30222/30557-1nM
30222/30558 1nM
siGL2-10nM
Inv siGL2-10nM
30222/30224-10nM
30222/30551-10nM
30222/30557-10nM
30222/30558 10nM
30222/30546 10nM

Figure 15


Firefly/Renilla X 100
0
1
2
3
4
5
6
7
8
siRNA
Cells
siGL2-1nM
Inv siGL2-1nM
30063/30430-1nM
30434/30430-1nM
30435/30430-1nM
siGL2-10nM
Inv siGL2-10nM
30063/30430-10nM
30434/30430-10nM
30435/30430-10nM

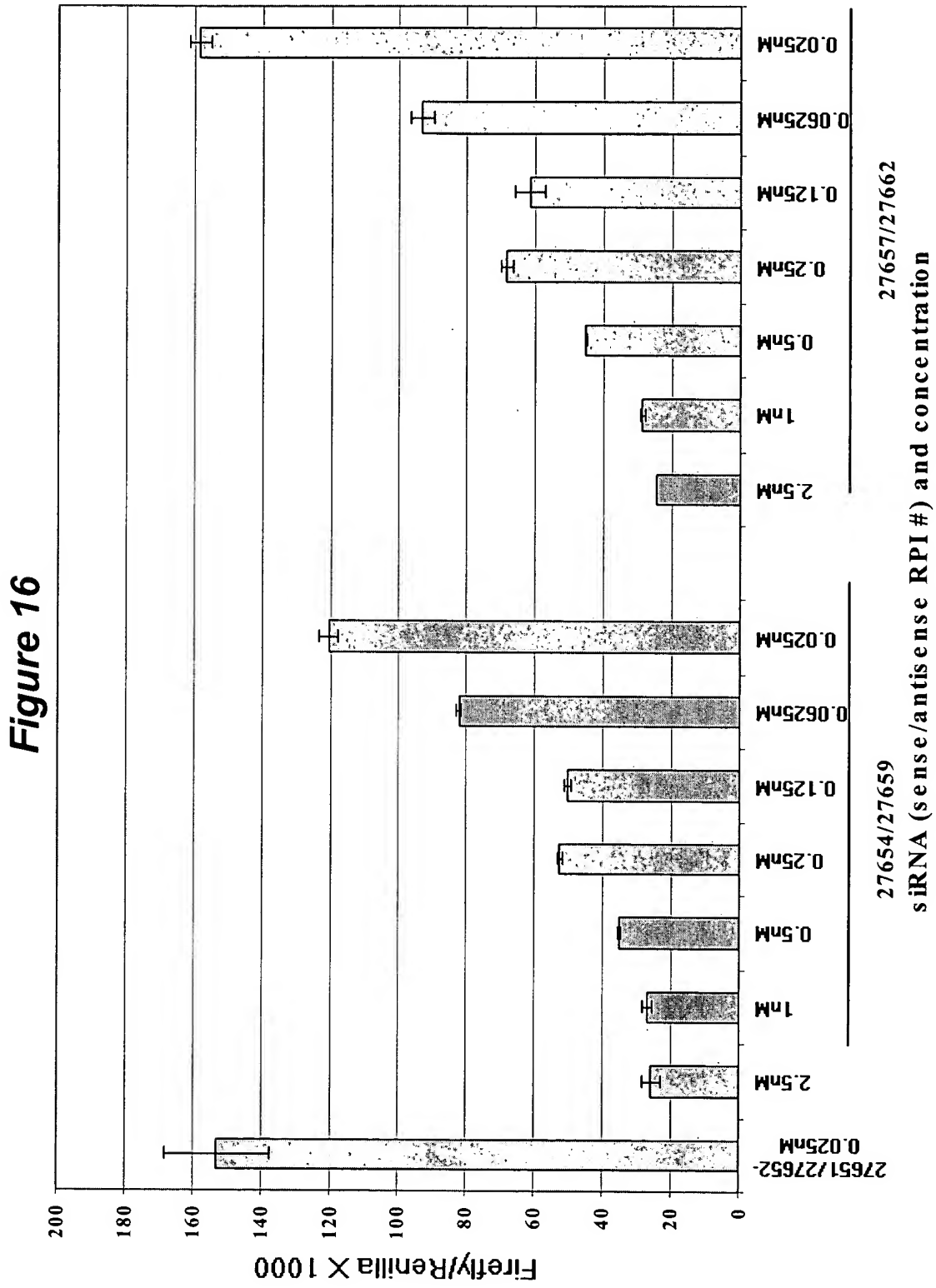
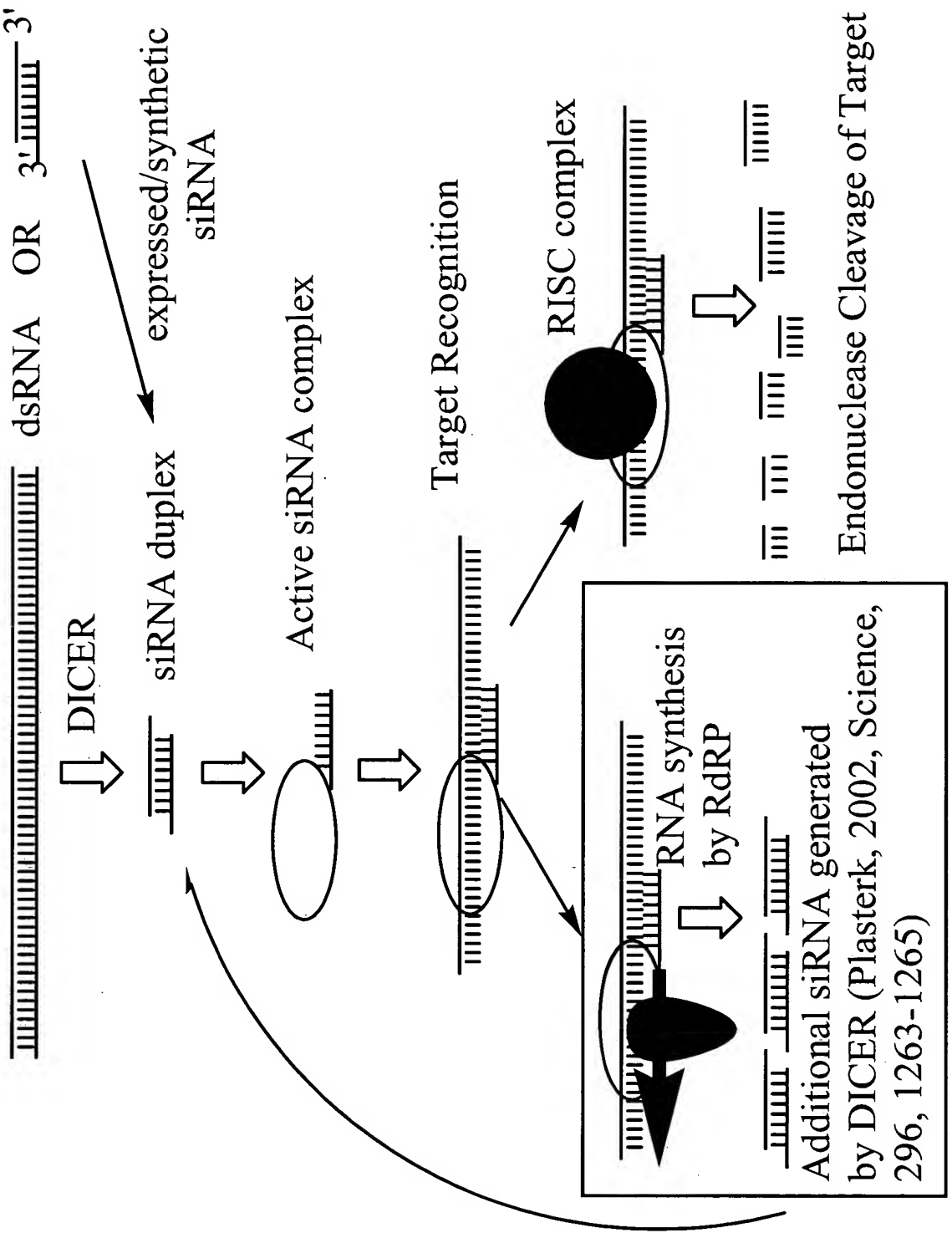
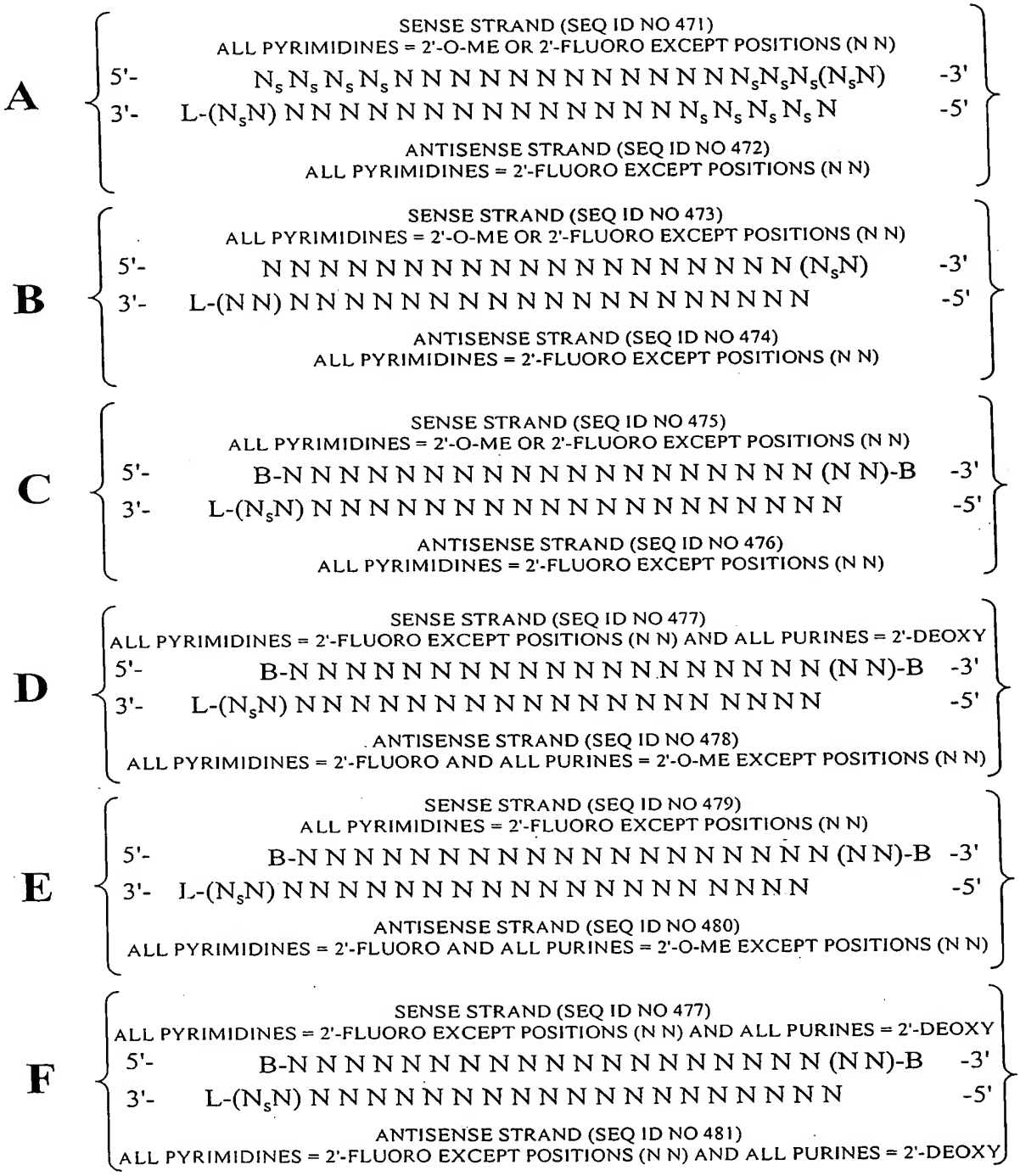


Figure 16
Firefly/Renilla X 1000
200
180
160
140
120
100
80
60
40
20
0
27651/27652-
0.025nM
2.5nM
1nM
0.5nM
0.25nM
0.125nM
0.0625nM
0.025nM
27654/27659
2.5nM
1nM
0.5nM
0.25nM
0.125nM
0.0625nM
0.025nM
27657/27662
siRNA (sense/antisense RPI #) and concentration

*Figure 17*


dsRNA OR 3' 3'
DICER
siRNA duplex
expressed/synthetic siRNA
Active siRNA complex
Target Recognition
RISC complex
RNA synthesis by RdRP
Additional siRNA generated by DICER (Plasterk, 2002, Science, 296, 1263-1265)
Endonuclease Cleavage of Target

# *Figure 18*




POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES
B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENT
L = GLYCERYL MOIETY THAT IS OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

# *Figure 19*

**A**

SENSE STRAND (SEQ ID NO 482)

5'- $c_S c_S c_S c_S$G G G A G G u c u c G u $A_S G_S A_S T_S T$ -3'

3'- L-$T_S T$ G G G G *c c c u c c* A G A G $c_S A_S u_S c_S u$ -5'

ANTISENSE STRAND (SEQ ID NO 483)

**B**

SENSE STRAND (SEQ ID NO 484)

5'- c c c c G G G A G G u c u c G u A G A $T_S T$ -3'

3'- L-*T T* G G G G *c c c u c c* A G A G *c* A *u c u* -5'

ANTISENSE STRAND (SEQ ID NO 485)

**C**

SENSE STRAND (SEQ ID NO 486)

5'- iB-c c c c G G G A G G u c u c G u A G A *T T*-iB -3'

3'- L-$T_S T$ G G G G *c c c u c c* A G A G *c* A *u c u* -5'

ANTISENSE STRAND (SEQ ID NO 487)

**D**

SENSE STRAND (SEQ ID NO 488)

5'- iB-*c c c c G G G A G G u c u c G u A G A T T*-iB -3'

3'- L-$T_S T$ g g g g c c c u c c a g a g c a u c u -5'

ANTISENSE STRAND (SEQ ID NO 489)

**E**

SENSE STRAND (SEQ ID NO 490)

5'- iB-*c c c c* G G G A G G *u c u c* G u A G A *T T*-iB -3'

3'- L-$T_S T$ g g g g c c c u c c a g a g c a u c u -5'

ANTISENSE STRAND (SEQ ID NO 491)

**F**

SENSE STRAND (SEQ ID NO 488)

5'- iB-*c c c c G G G A G G u c u c G u A G A T T*-iB -3'

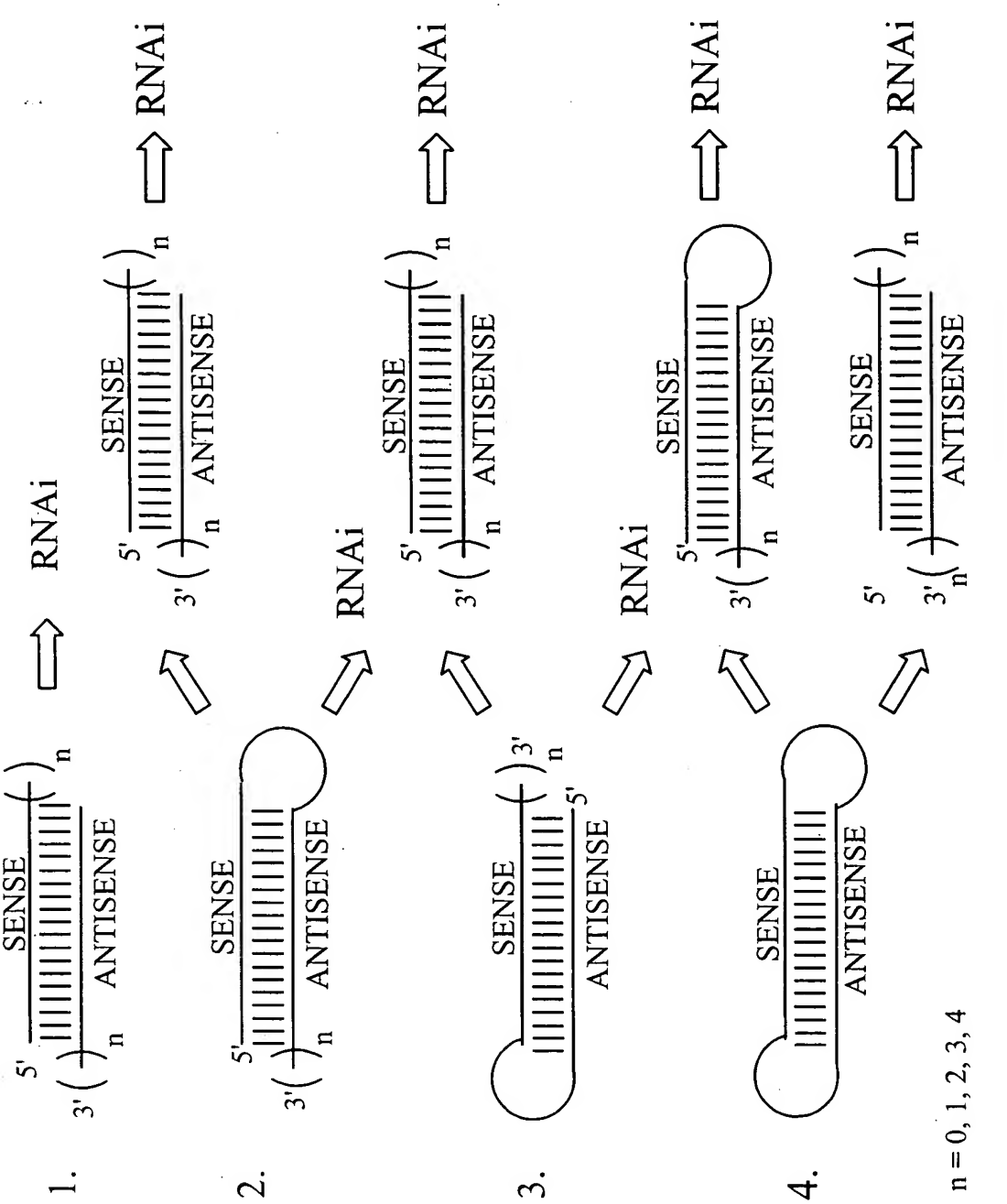
3'- L-$T_S T$ G G G G c c c u c c A G A G c A u c u -5'

ANTISENSE STRAND (SEQ ID NO 492)

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro
*italic lower case = 2'-deoxy-2'-fluoro*
underline = 2'-O-methyl

*ITALIC UPPER CASE = DEOXY*
B = INVERTED DEOXYABASIC
L = GLYCERYL MOIETY OPTIONALLY PRESENT
S = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE

*Figure 20*



# *Figure 21: Target site Selection using siRNA*

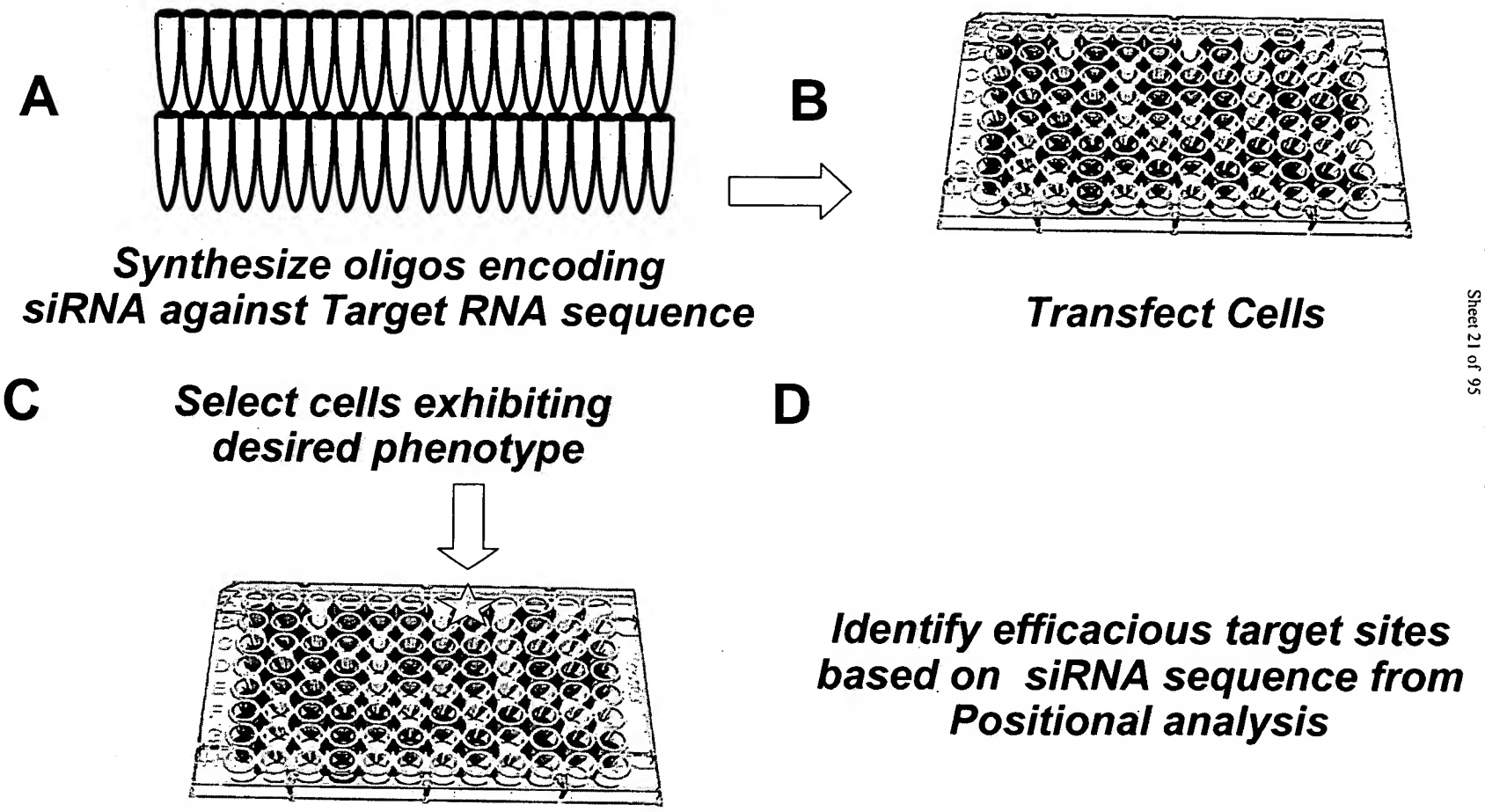
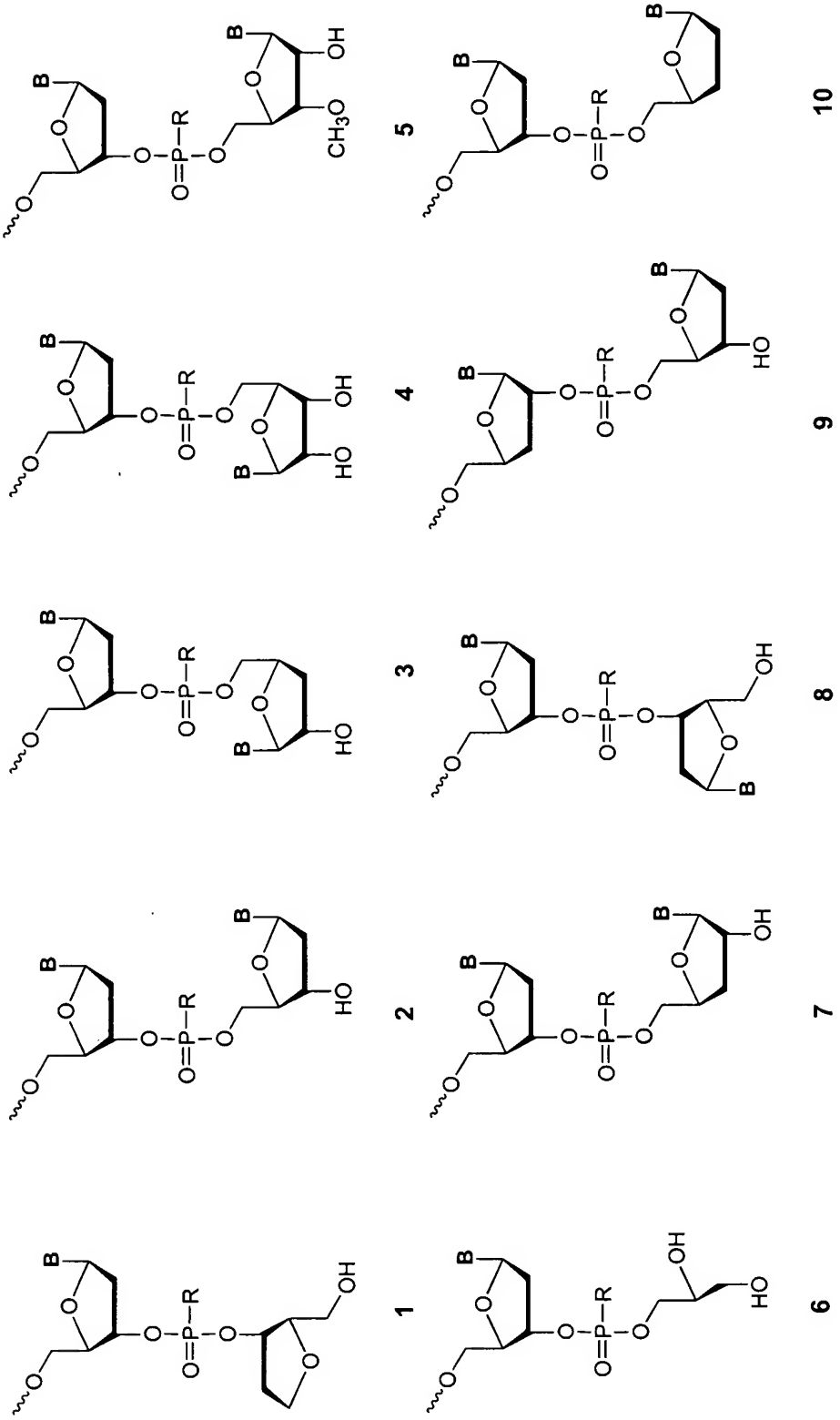


*Figure 22*




R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

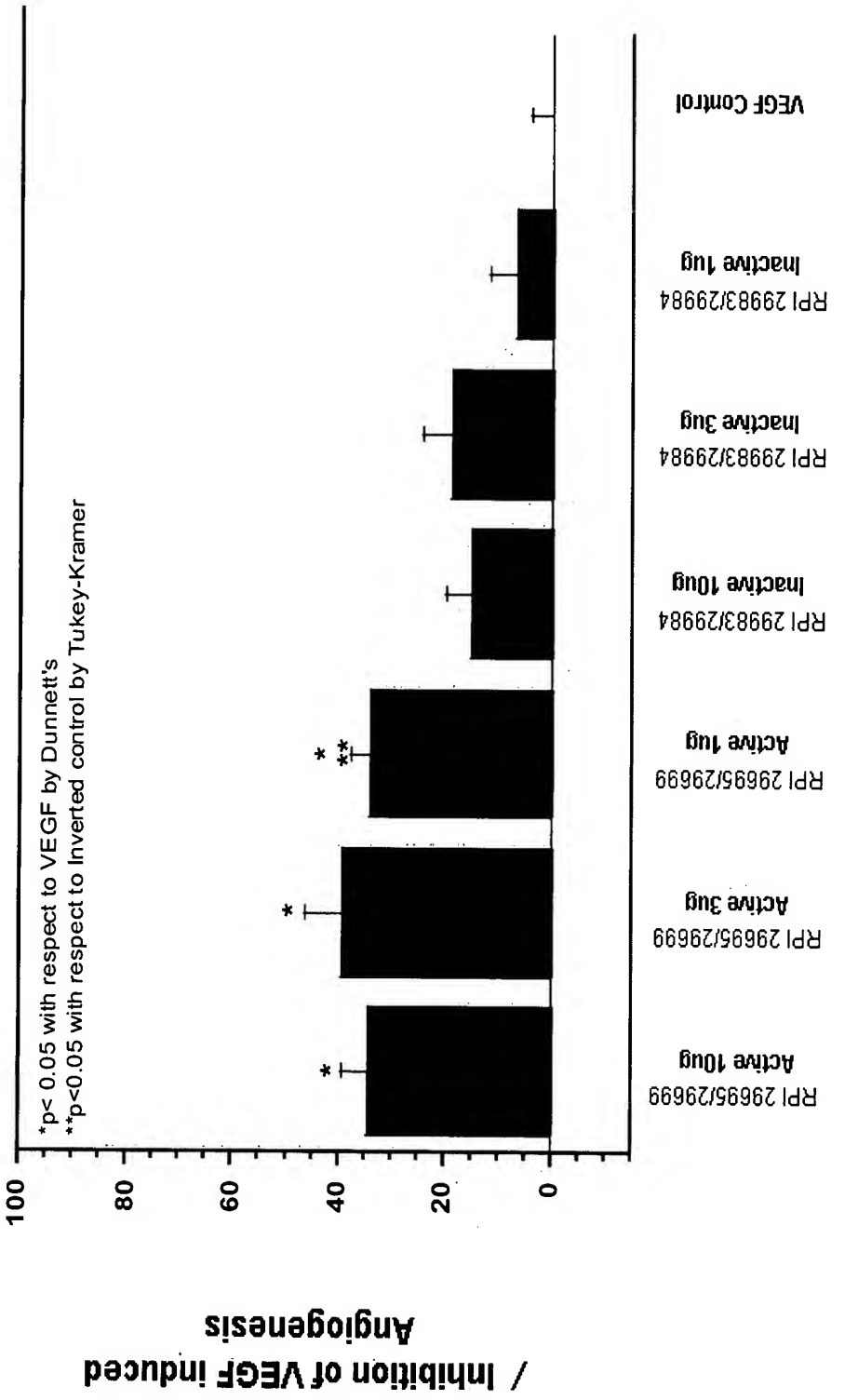



*Figure 23: Inhibition of VEGF-Induced Angiogenesis by siRNAs*

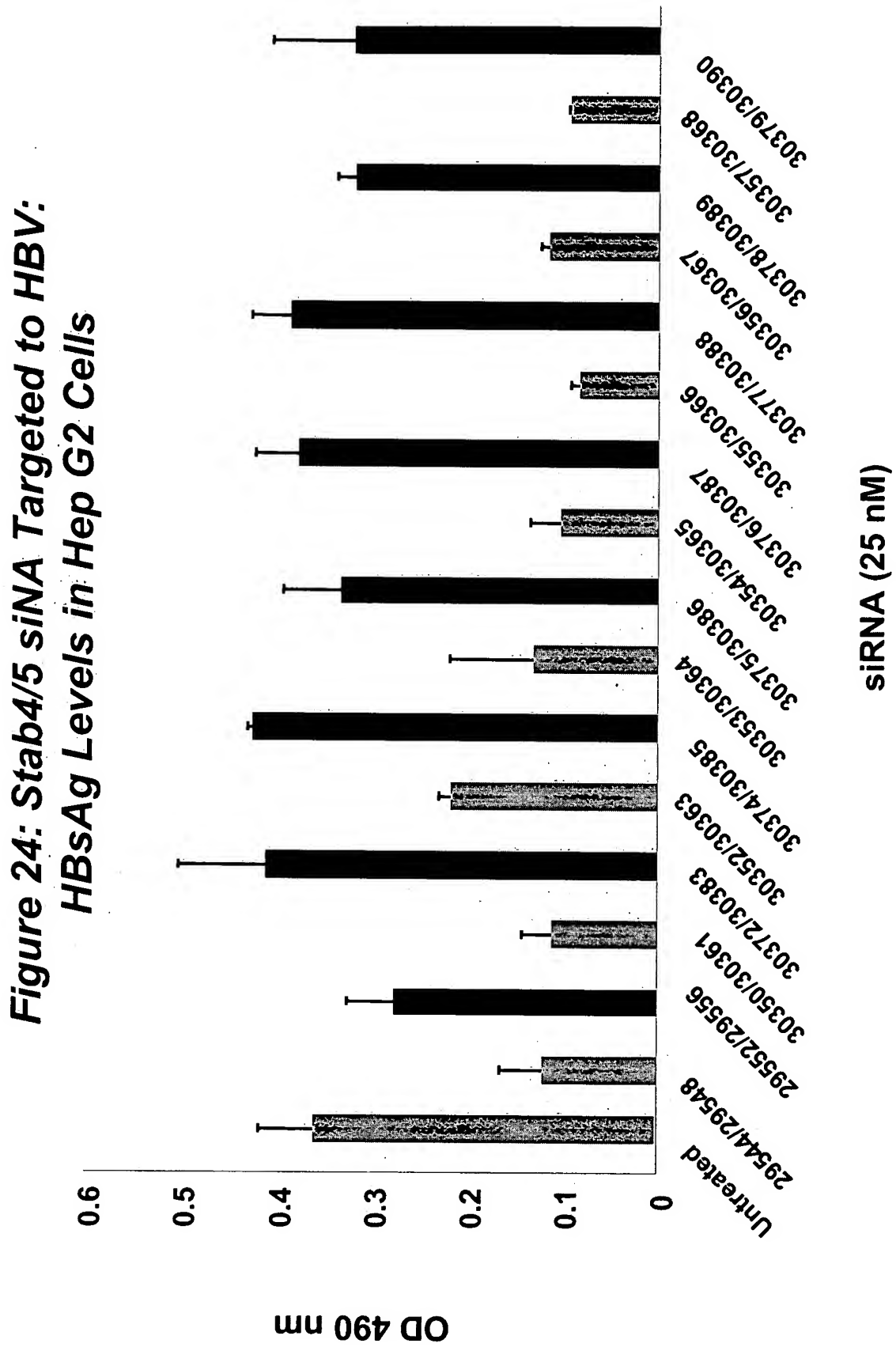



*Figure 24: Stab4/5 siNA Targeted to HBV: HBsAg Levels in Hep G2 Cells*

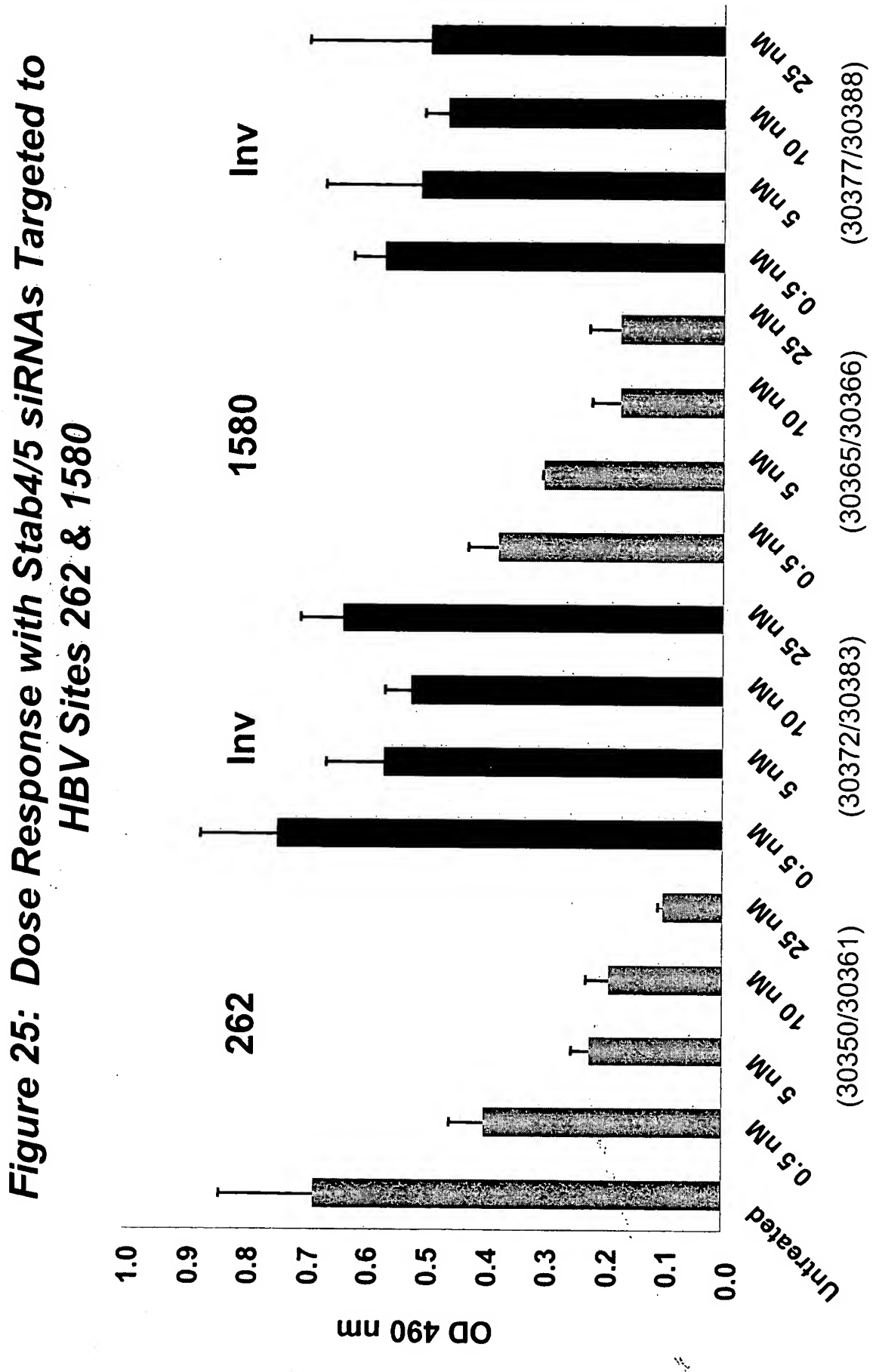


Figure 25: Dose Response with Stab4/5 siRNAs Targeted to HBV Sites 262 & 1580
OD 490 nm
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
262
Inv
1580
Inv
Untreated
0.5 nM
5 nM
10 nM
25 nM
(30350/30361)
(30372/30383)
(30365/30366)
(30377/30388)

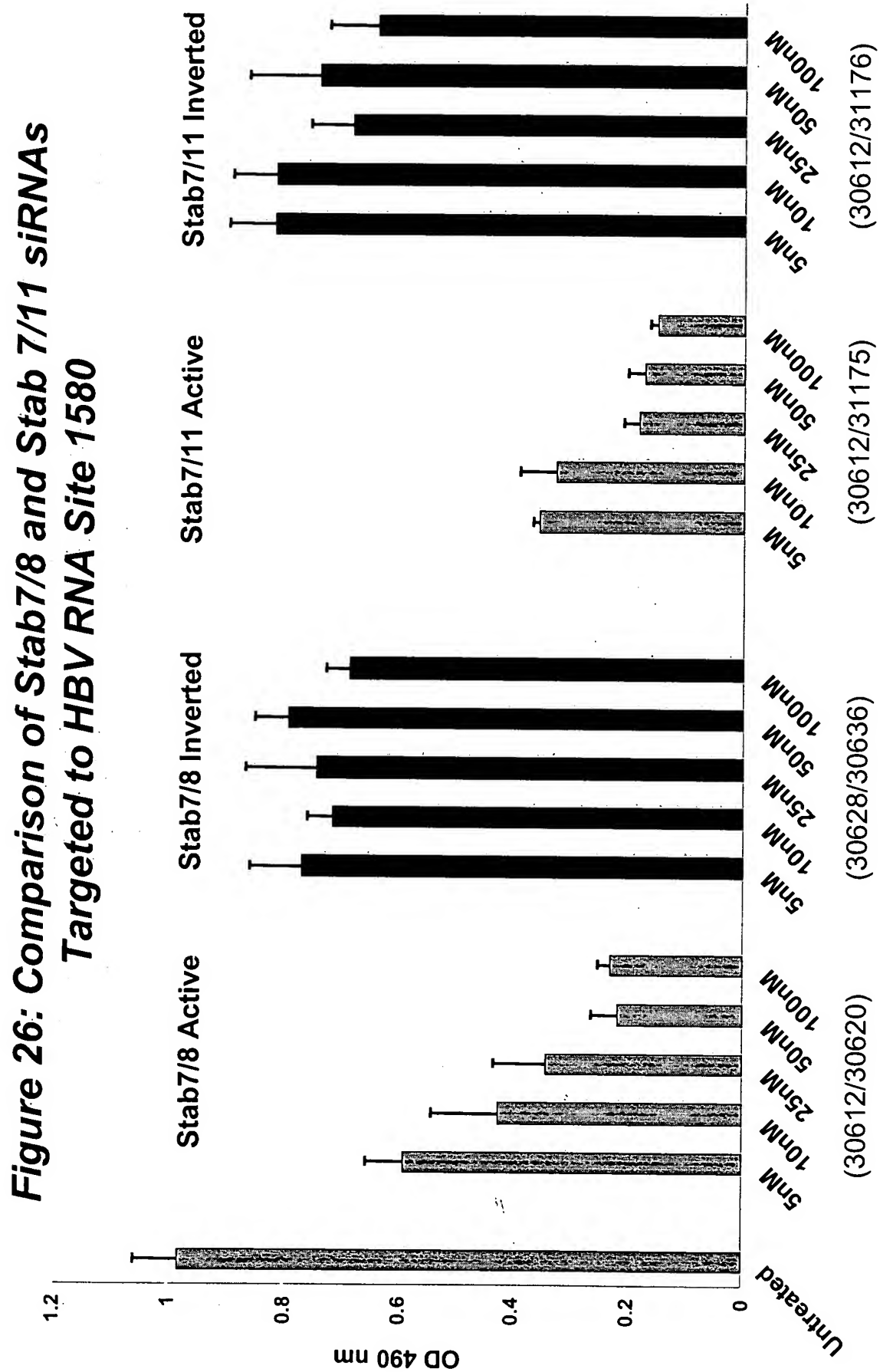


Figure 26: Comparison of Stab7/8 and Stab 7/11 siRNAs Targeted to HBV RNA Site 1580
OD 490 nm
1.2
1
0.8
0.6
0.4
0.2
0
Untreated
5nM
10nM
25nM
50nM
100nM
Stab7/8 Active
Stab7/8 Inverted
Stab7/11 Active
Stab7/11 Inverted
(30612/30620)
(30628/30636)
(30612/31175)
(30612/31176)

*Figure 27: Modification Strategy*

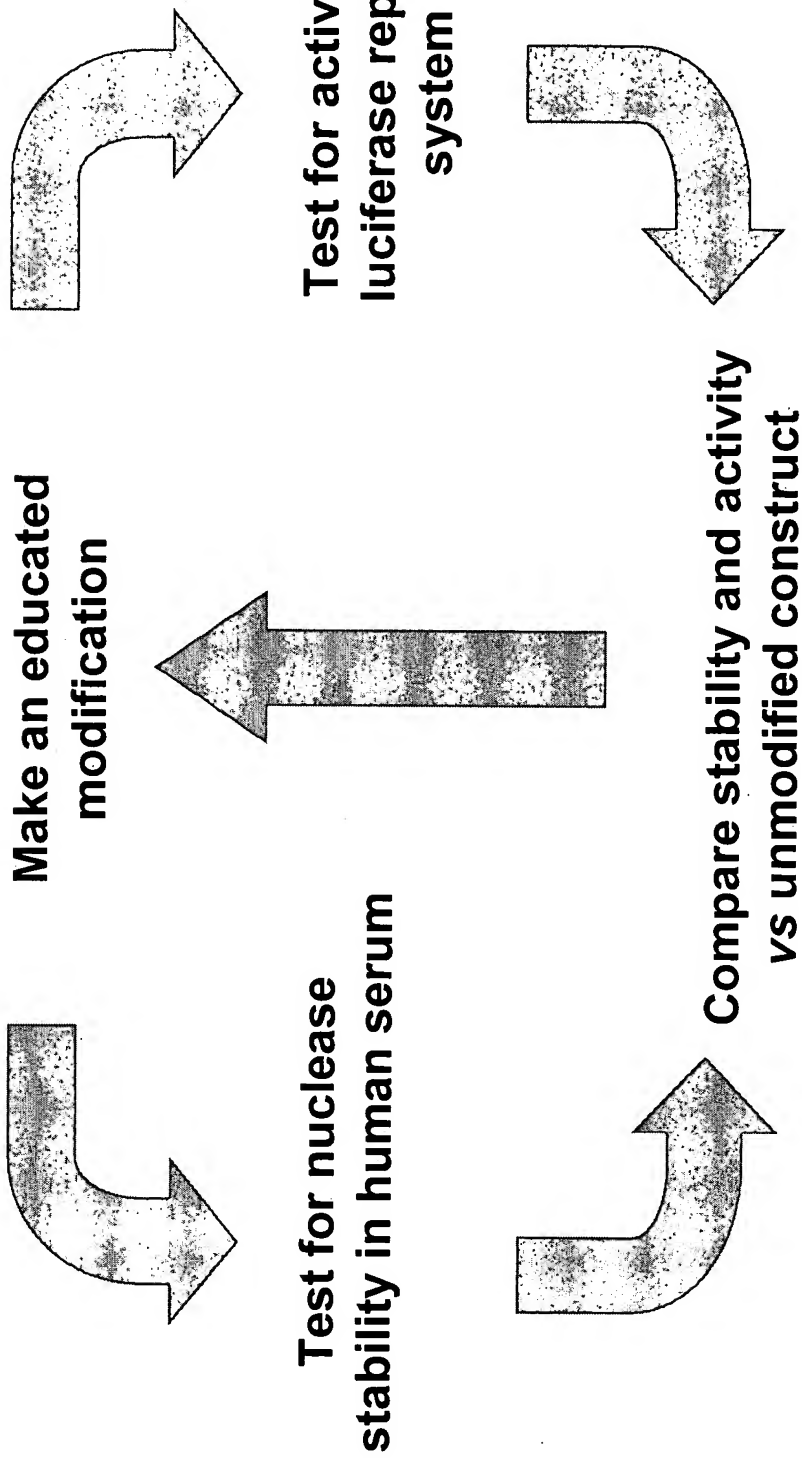


*Figure 28: Duration of siRNA Effect*
*All-Ribo vs. Stab4/5 HBV Site 1580: HBsAg Levels*

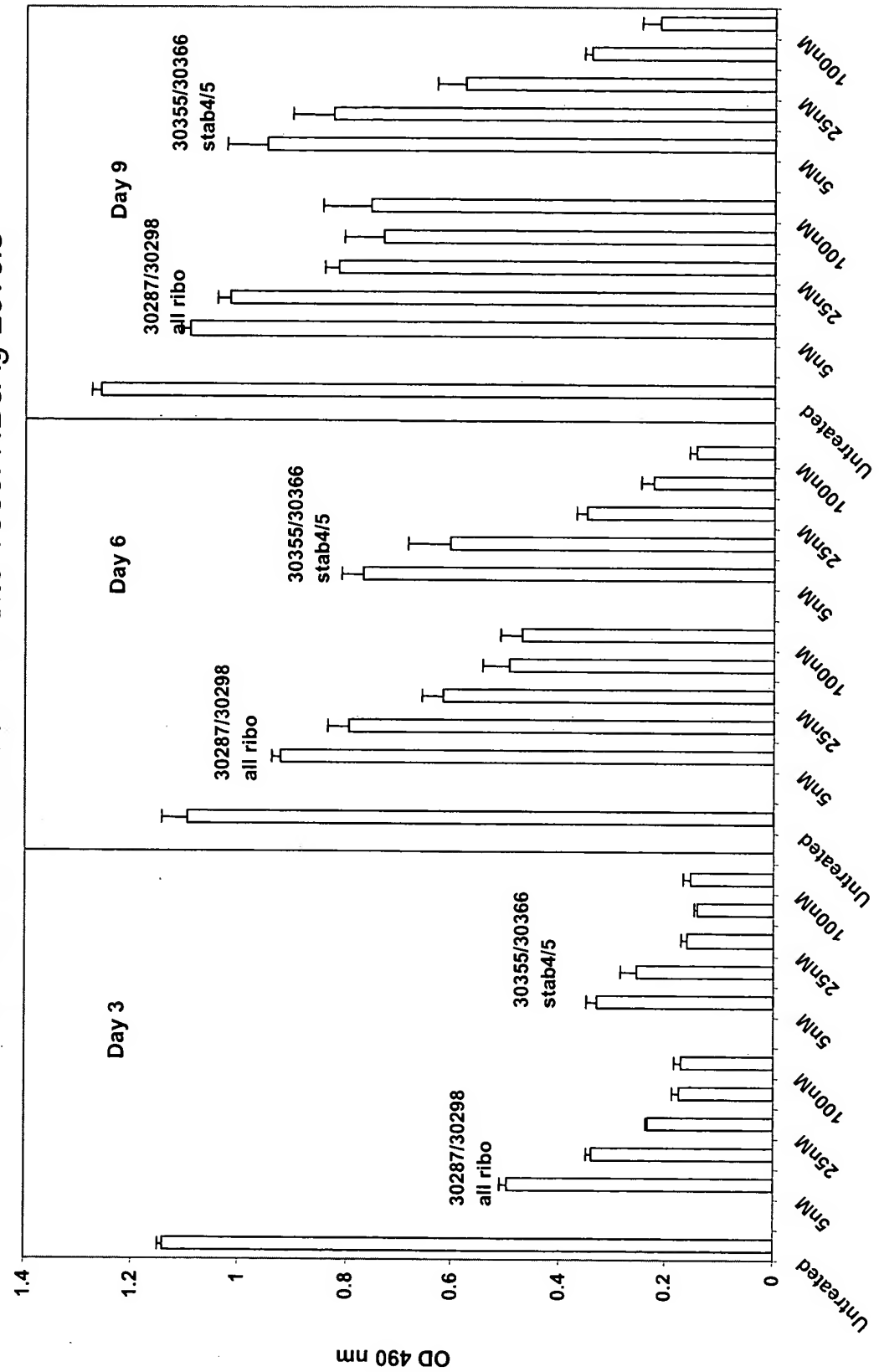


*Figure 29: Duration of siRNA Effect*
*All-Ribo vs. Stab7/8 HBV Site 1580: HBsAg Levels*

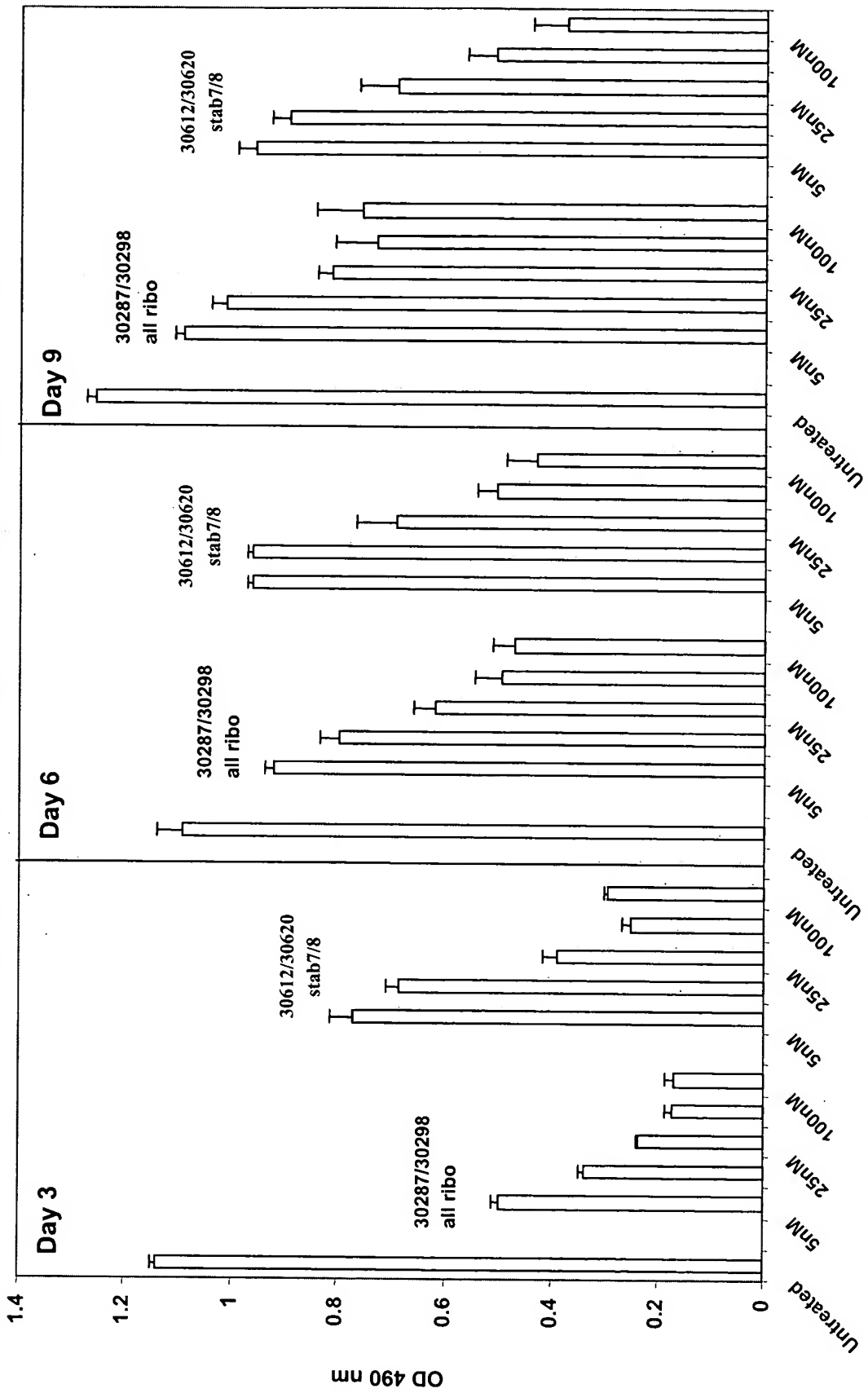


*Figure 30: Duration of siRNA Effect*
*All-Ribo vs. Stab7/11 HBV Site 1580: HBsAg Levels*

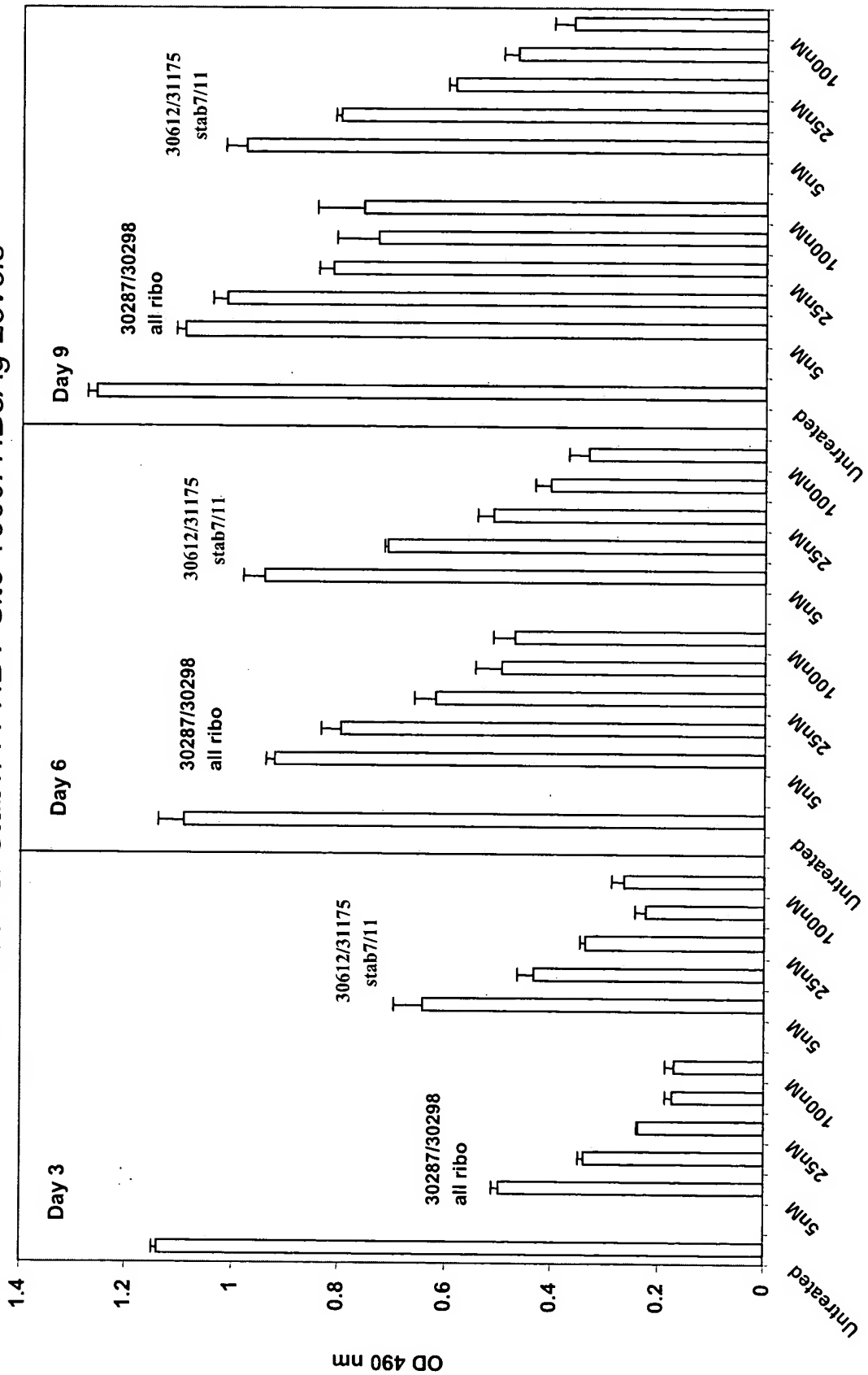


*Figure 31: Duration of siRNA Effect*
*All-Ribo vs. Stab9/10 HBV Site 1580: HBsAg Levels*

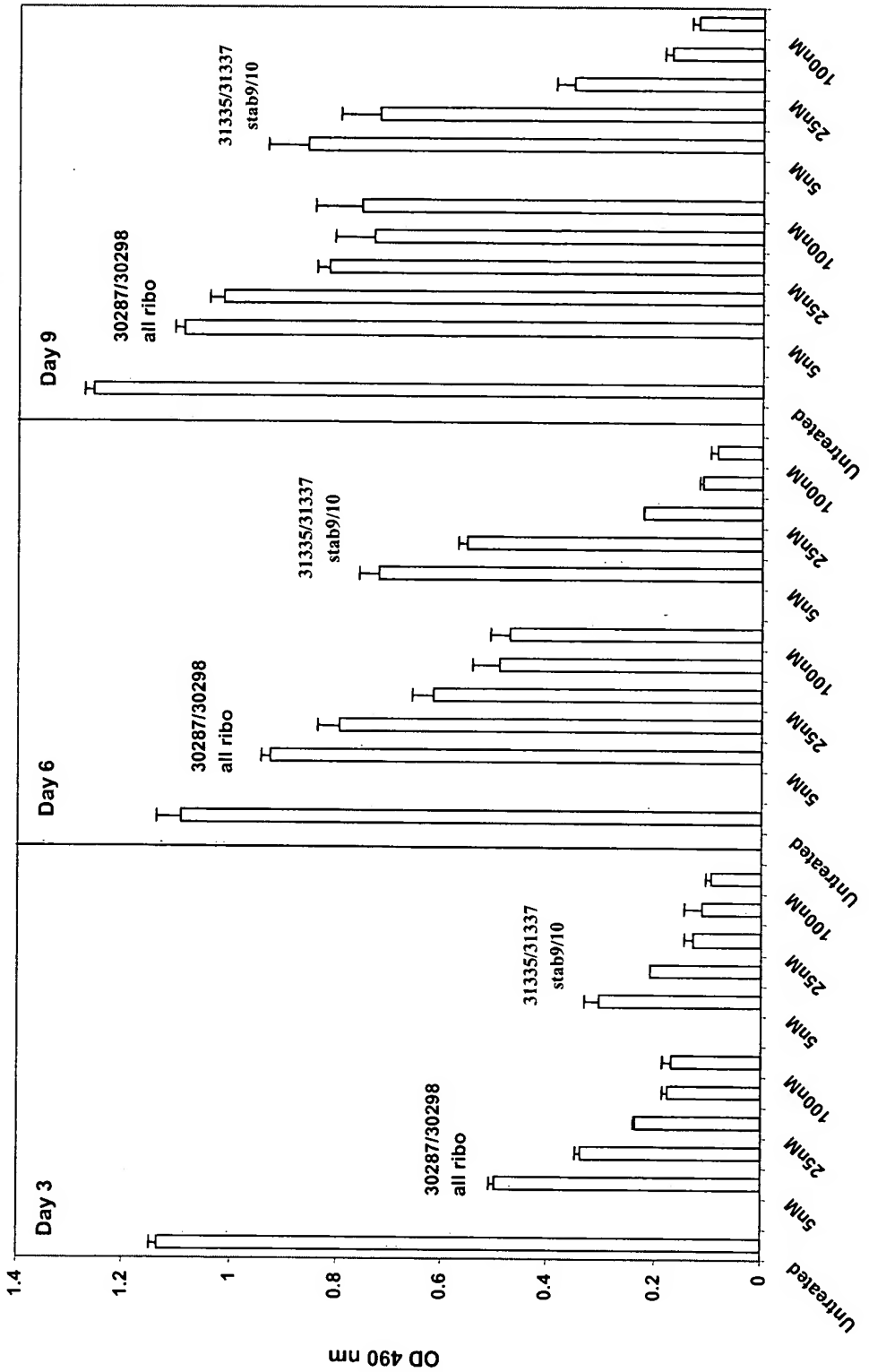


*Figure 32 : siRNAs targeting HCV chimera*

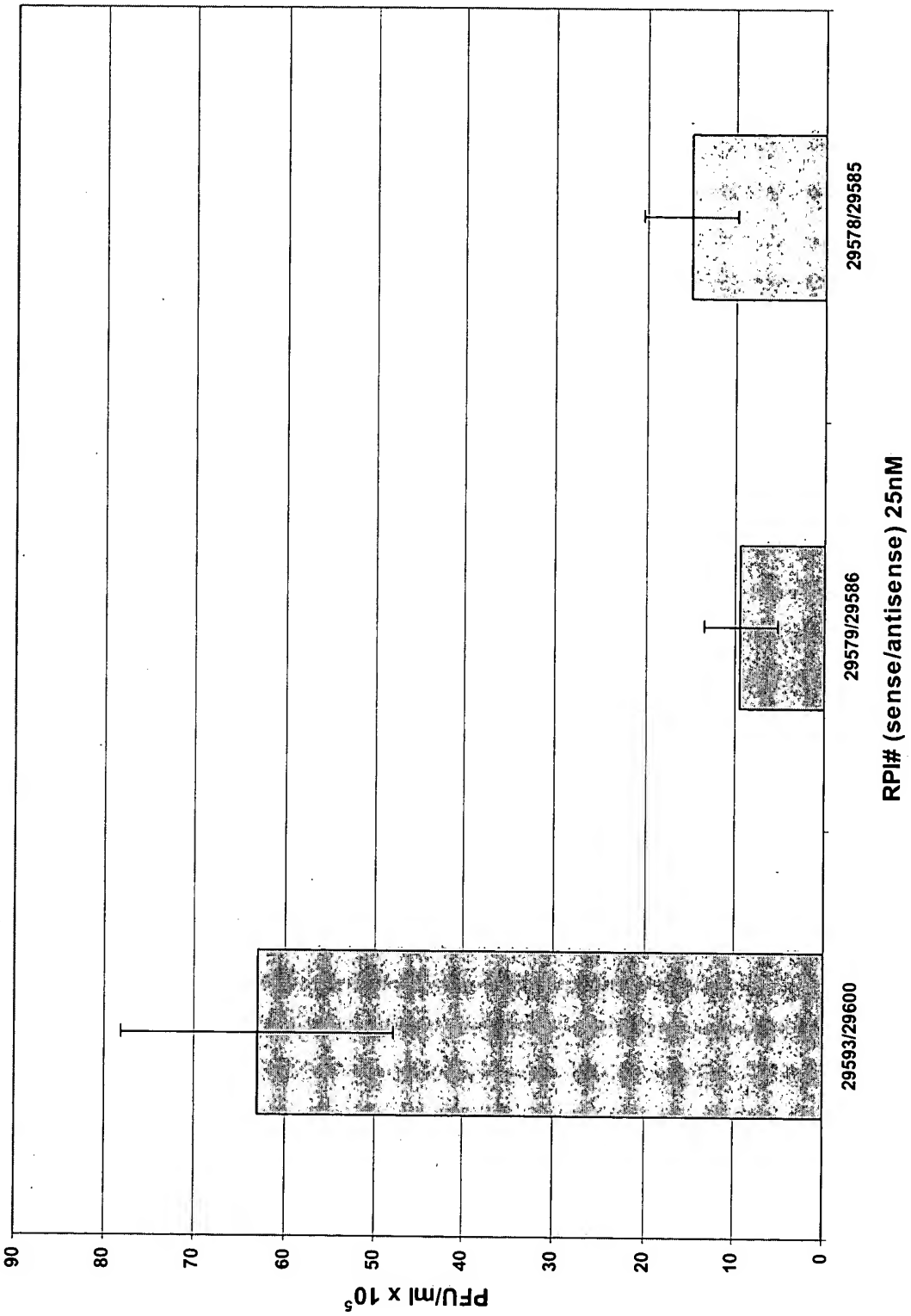


*Figure 33: HCV siRNA dose response*

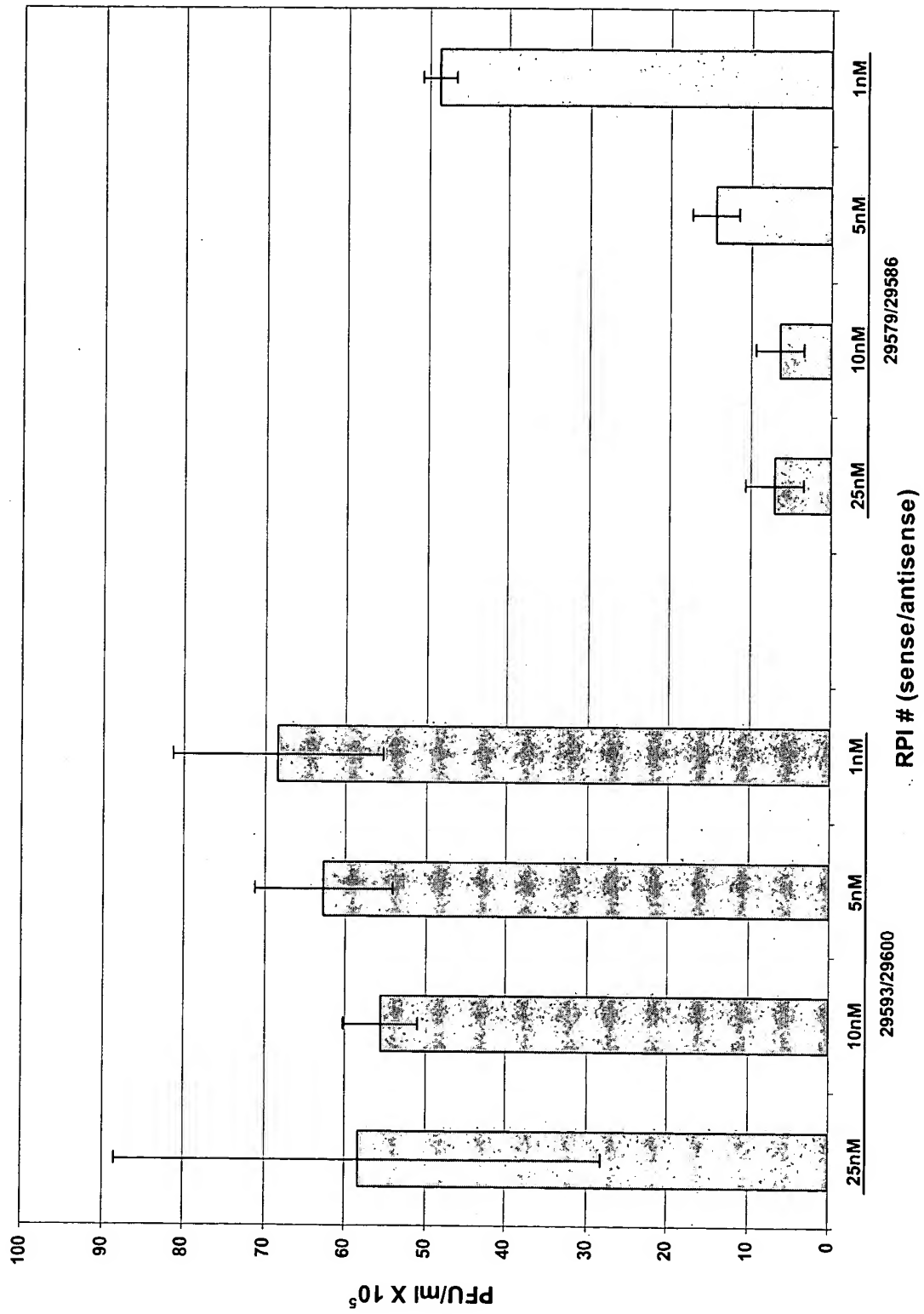


*Figure 34: Chemically Modified siRNA targeting HCV chimera*

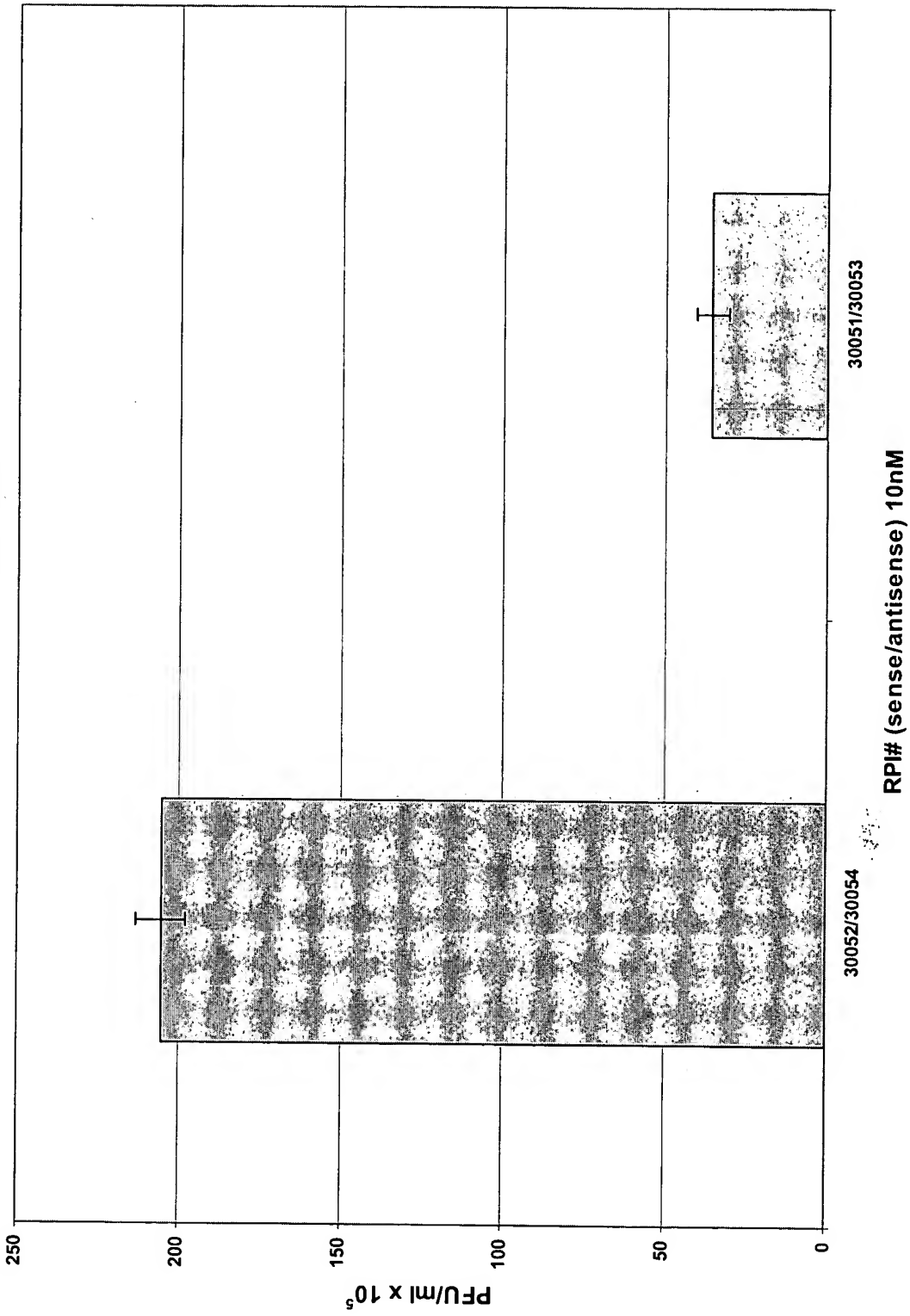


*Figure 35: Chemically Modified siRNA targeting HCV chimera*

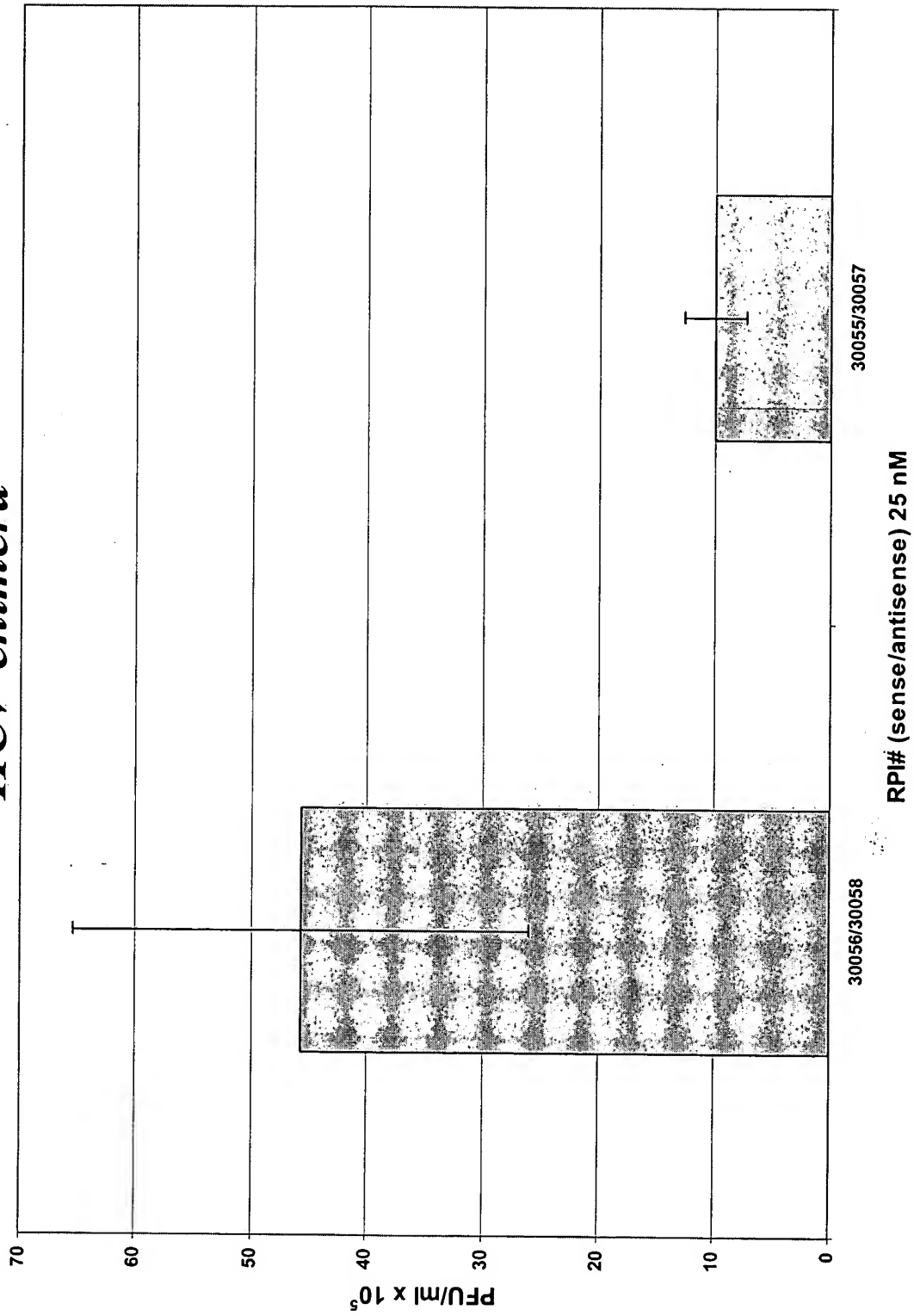


*Figure 36: Chemically Modified siRNA targeting HCV chimera*

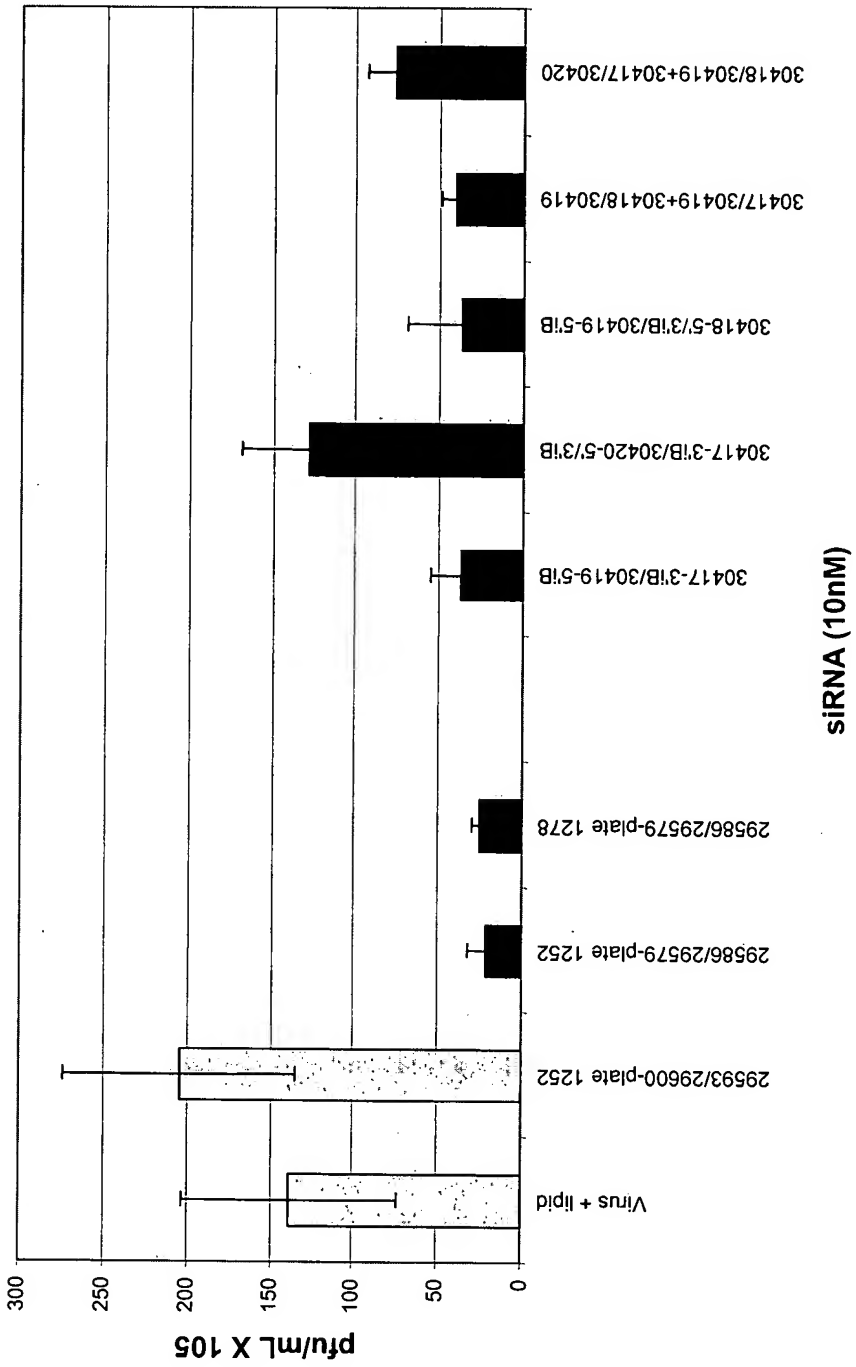
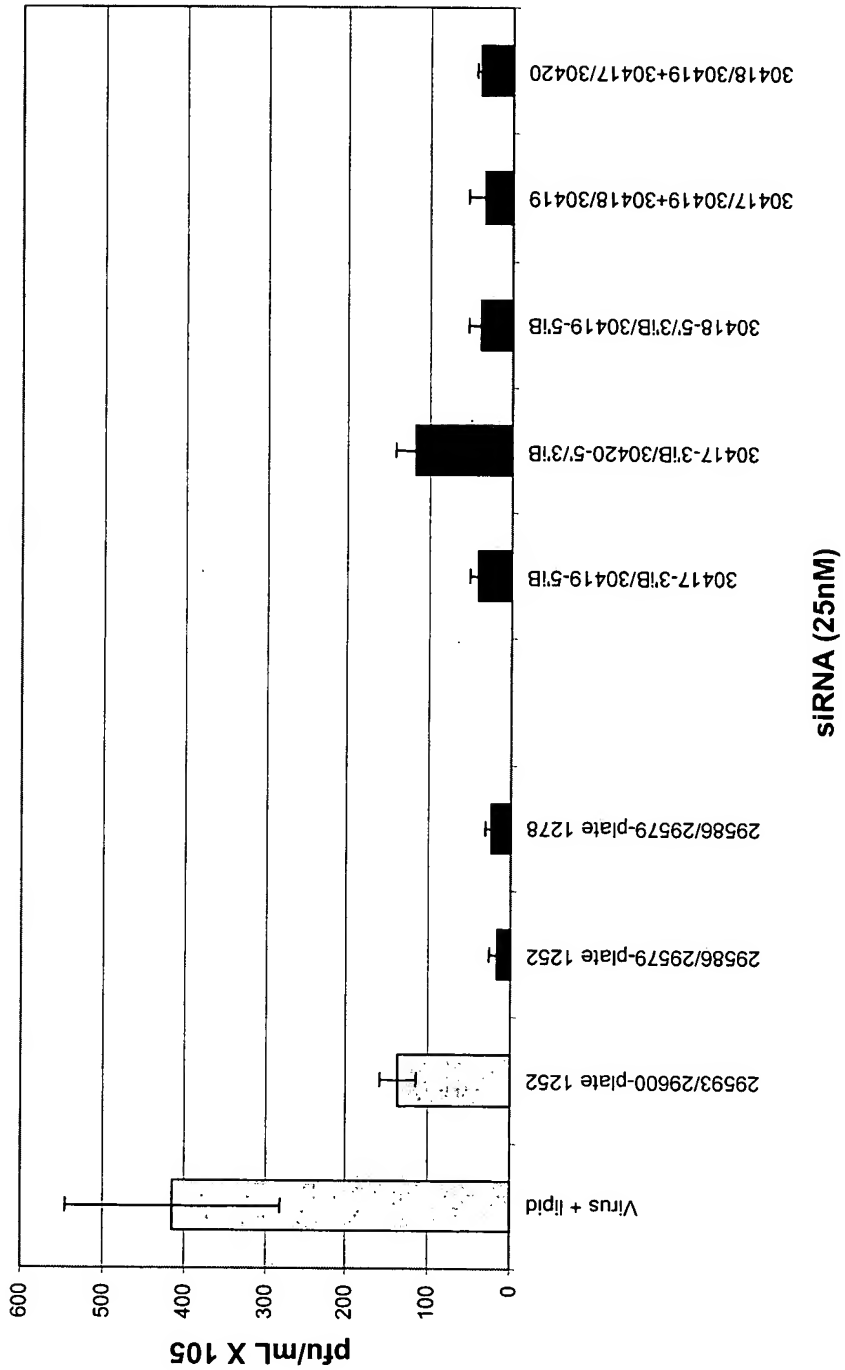


*Figure 37: Chemically Modified siRNA targeting HCV chimera*



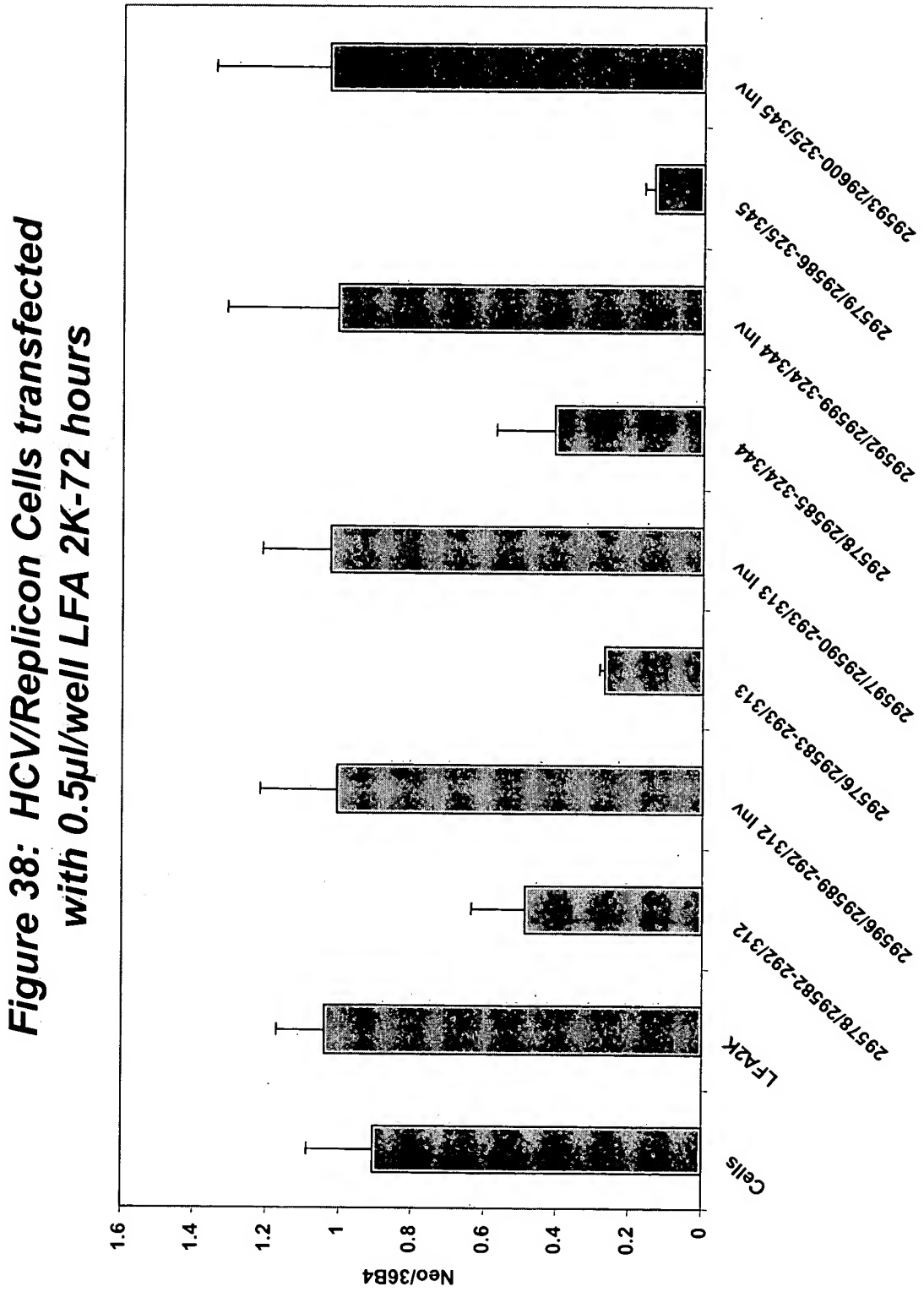



*Figure 38: HCV/Replicon Cells transfected with 0.5µl/well LFA 2K-72 hours*

*Figure 39: Dose Response with Stab4/5 siNA Leads in HCV Subgenomic Replicon*

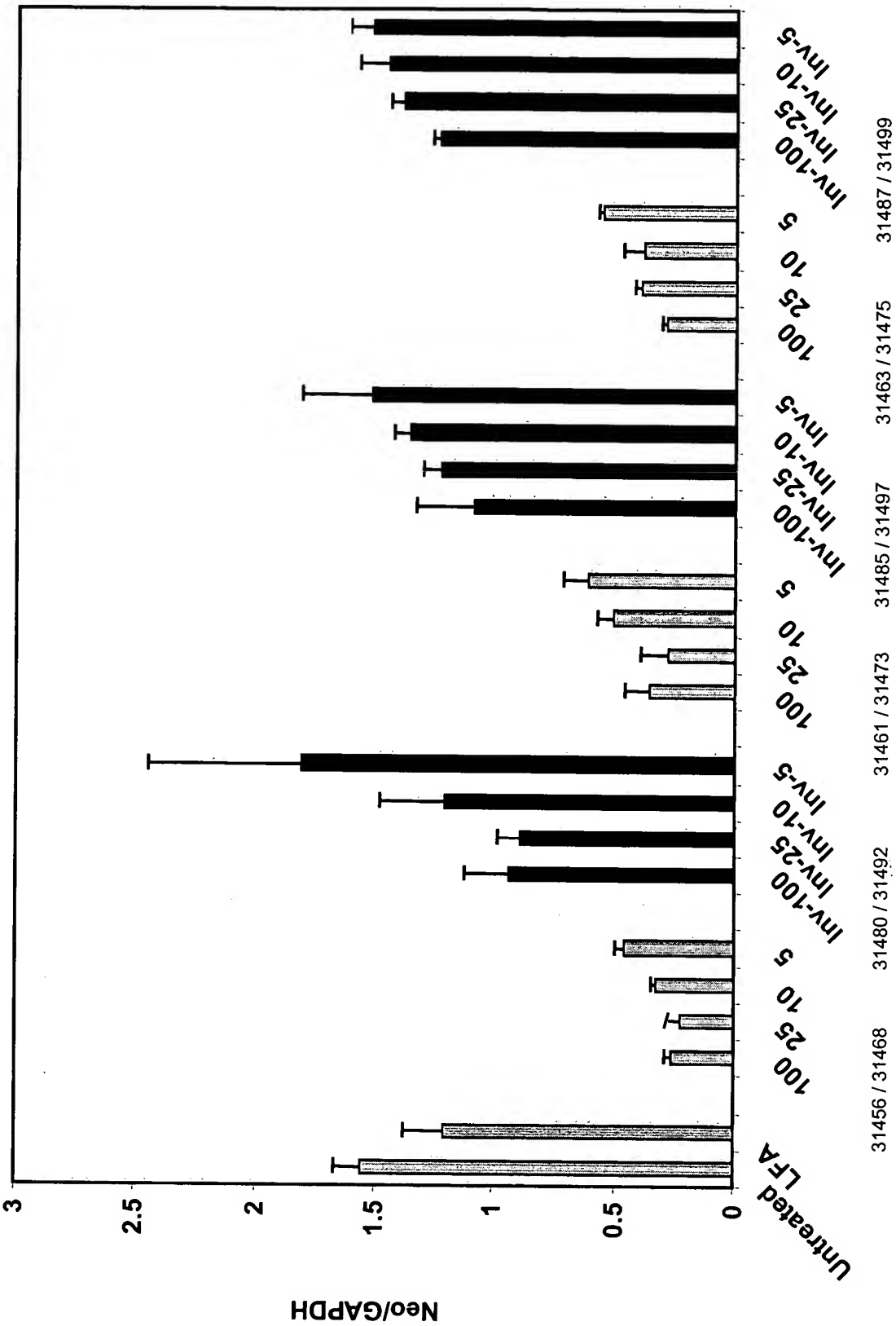


*Figure 40: Activity of Stab 7/8 siNA Leads in HCV Subgenomic Replicon*

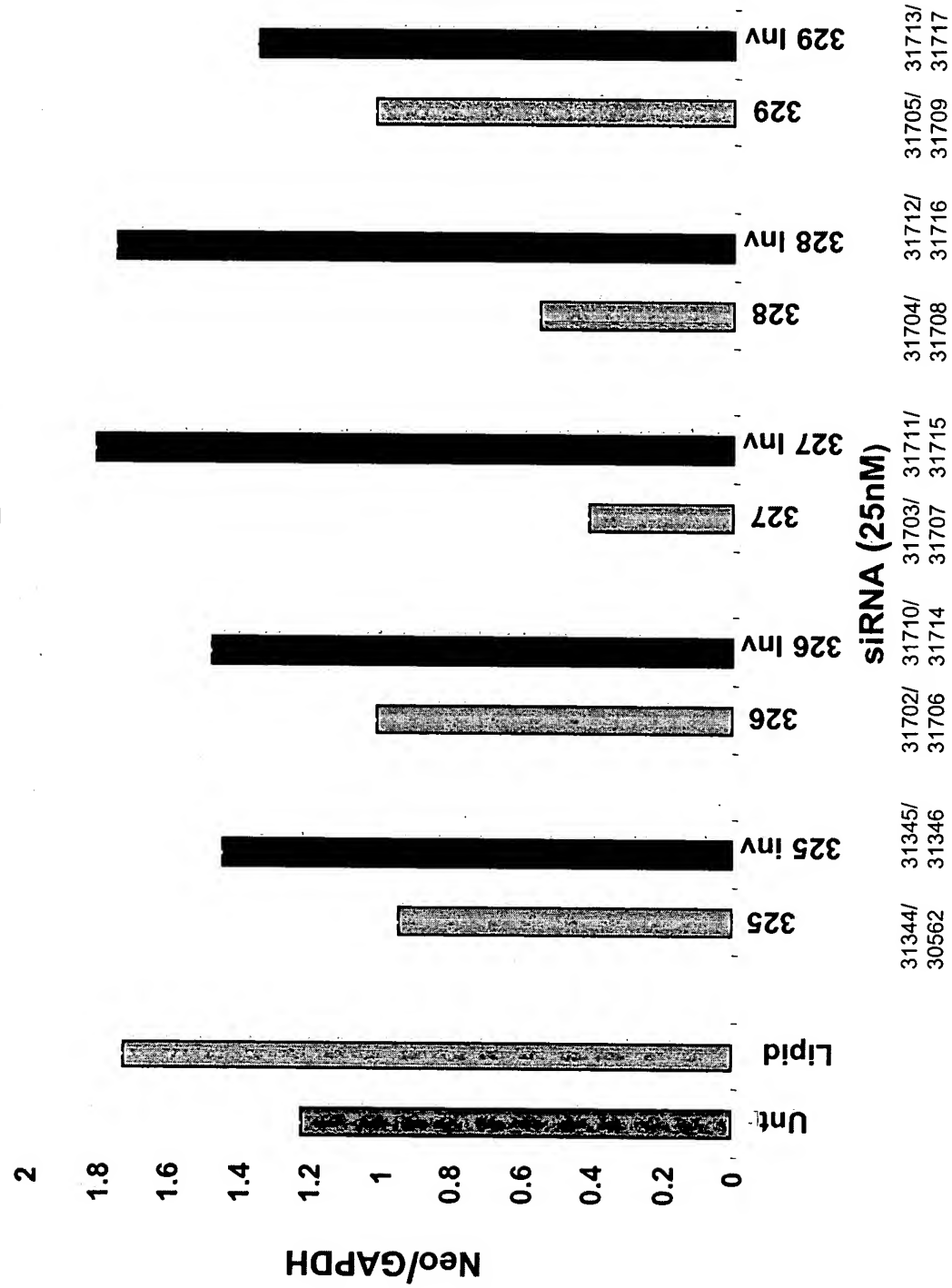


***Figure 41: Dose Response with Fully Modified HCV Site 327 siNA***

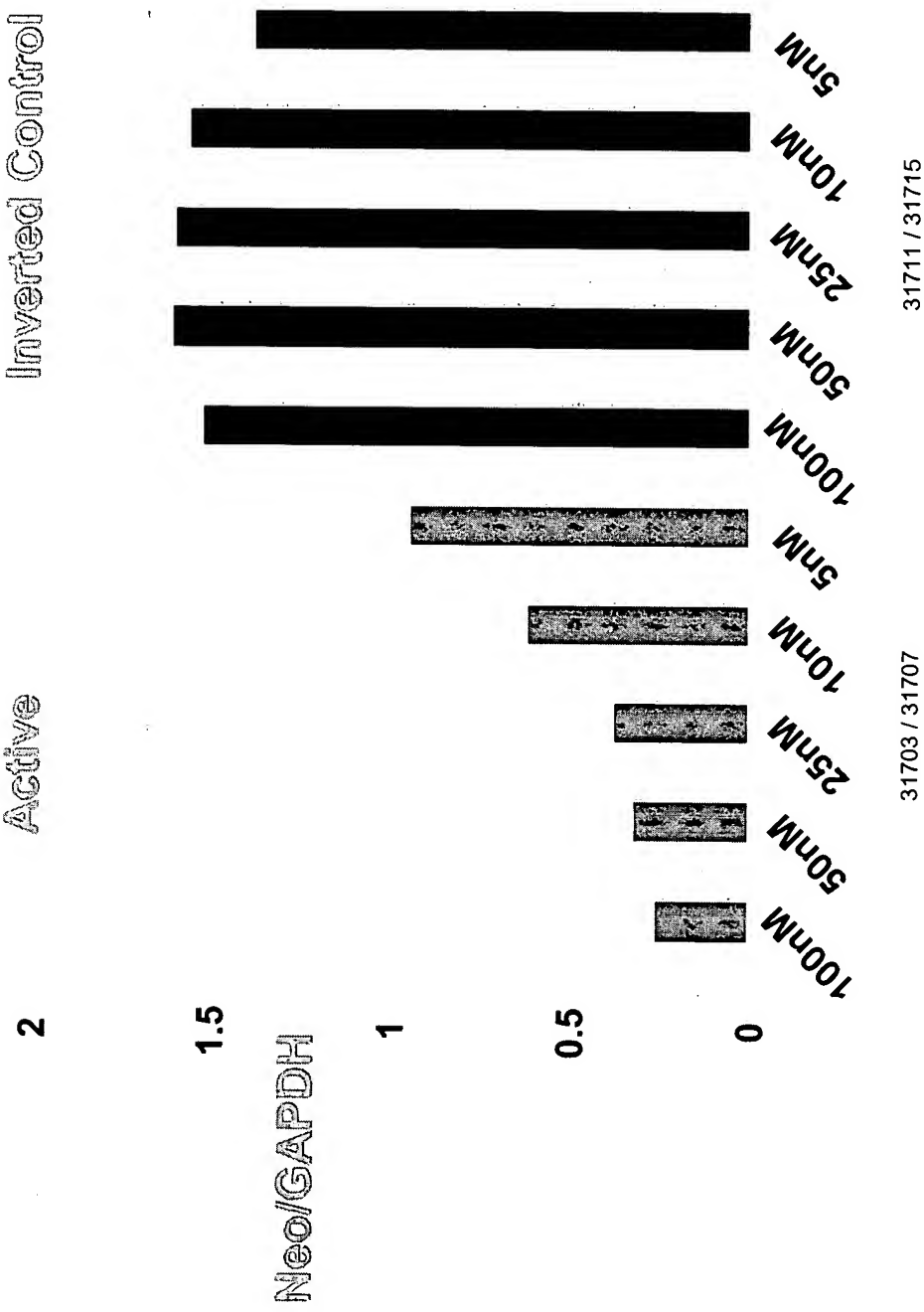


**Figure 42: Solid Phase Post-synthetic conjugation of pteroic acid**

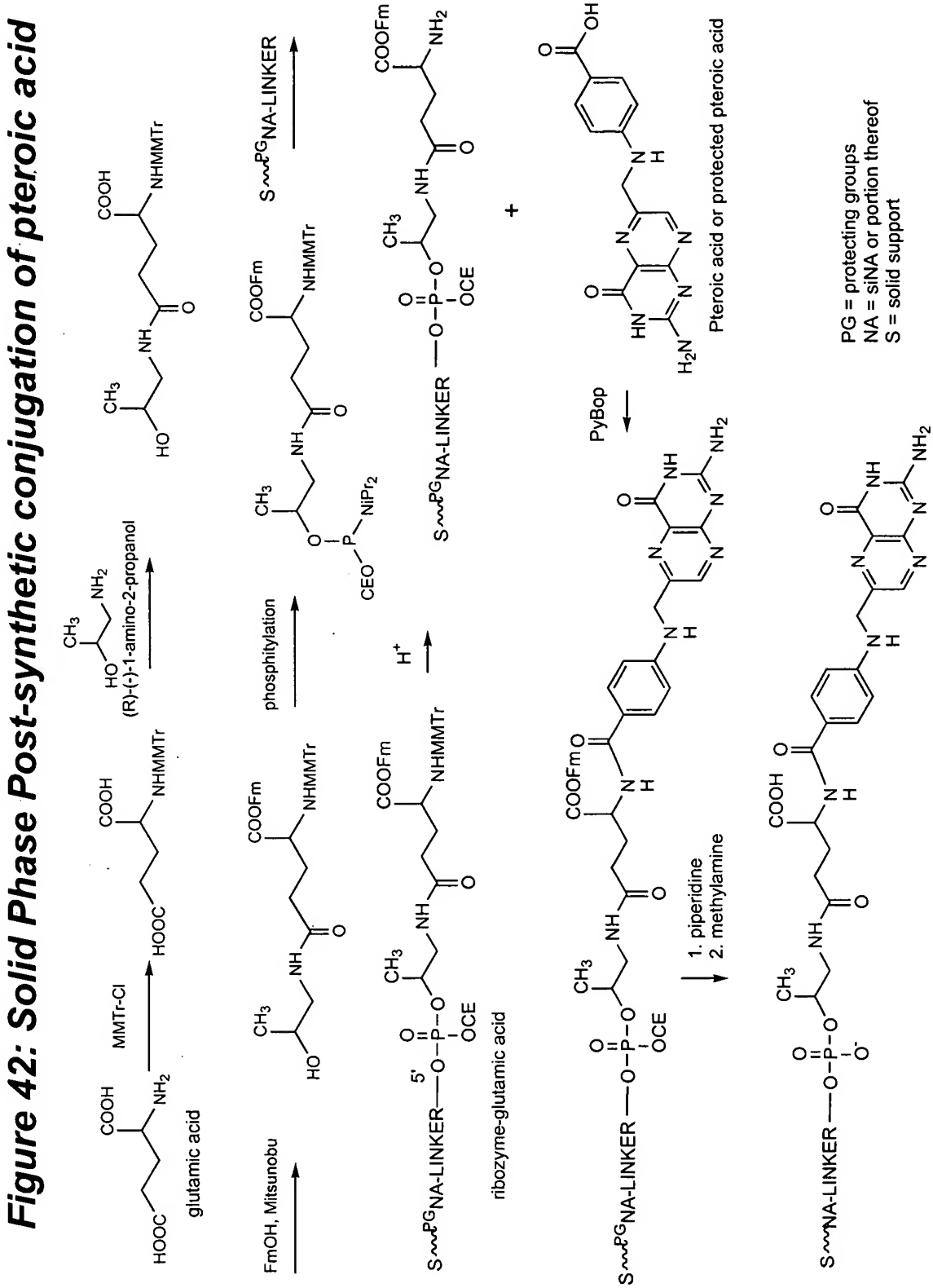
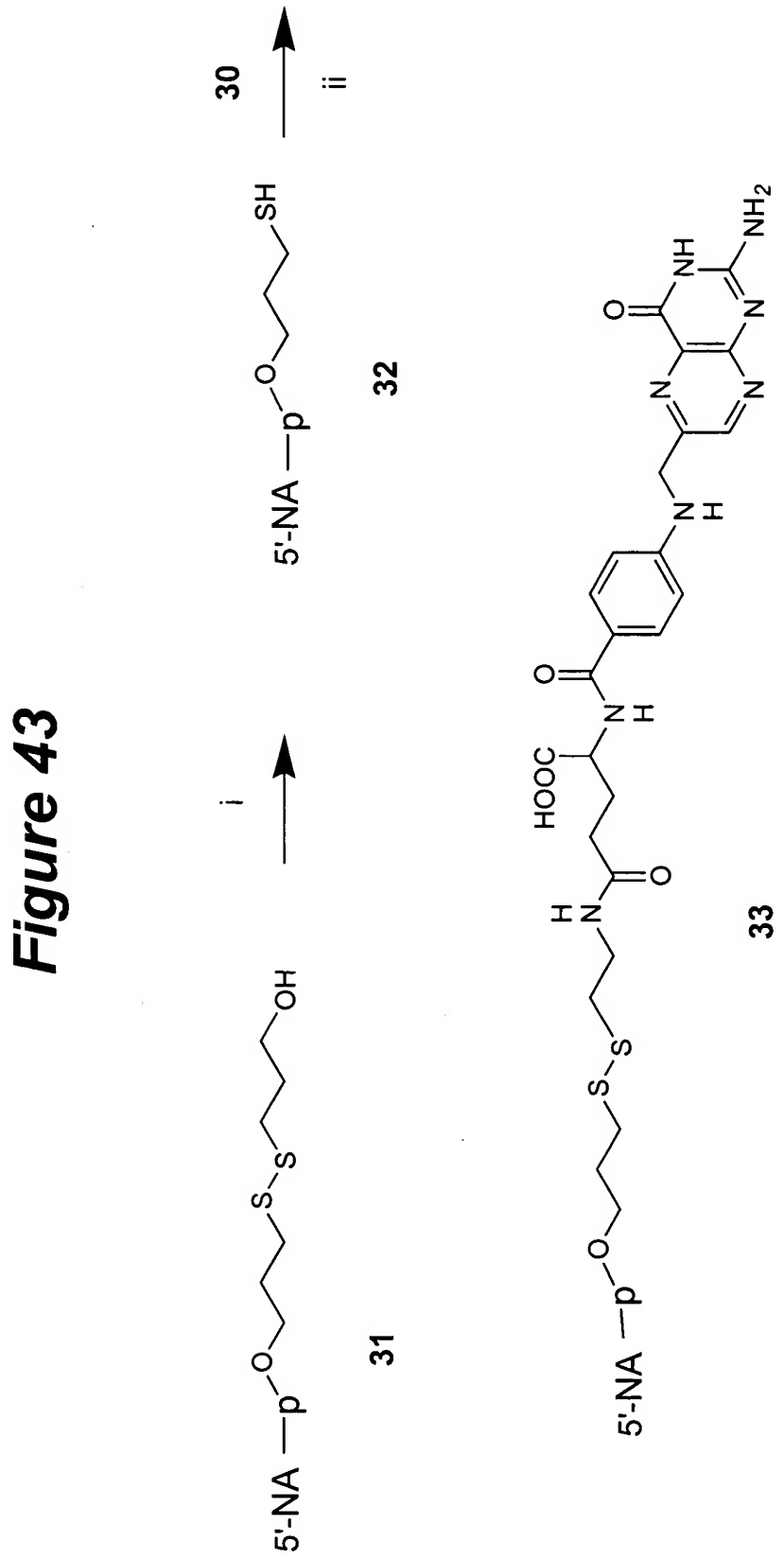
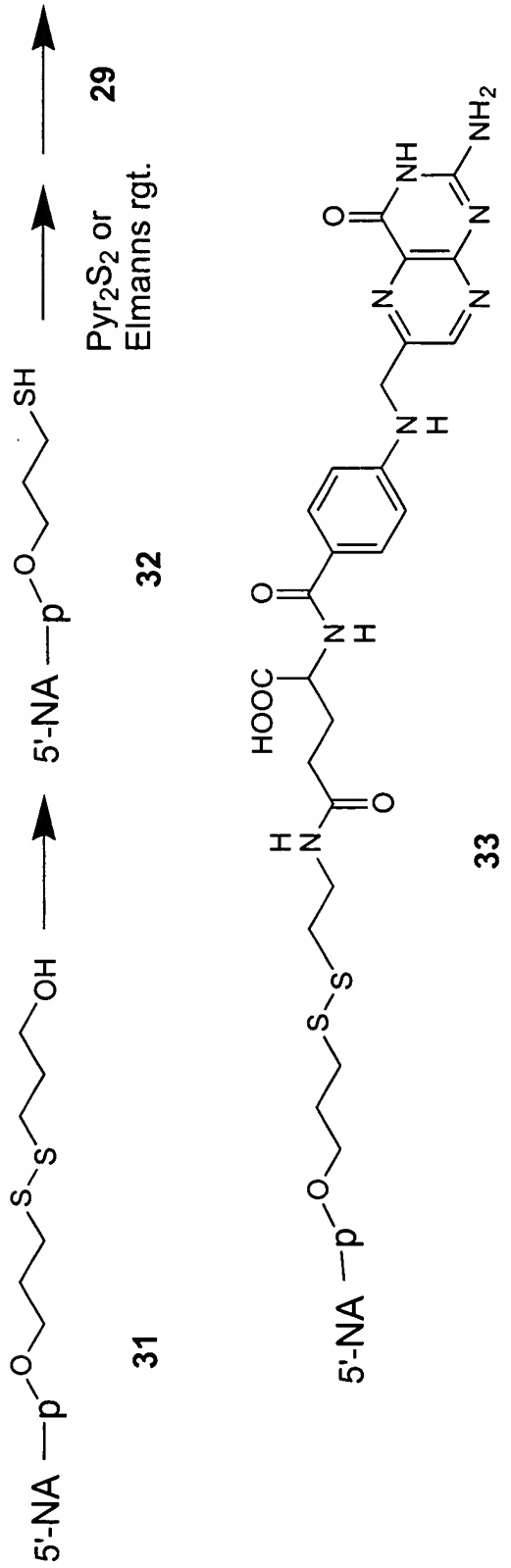


**Figure 43**



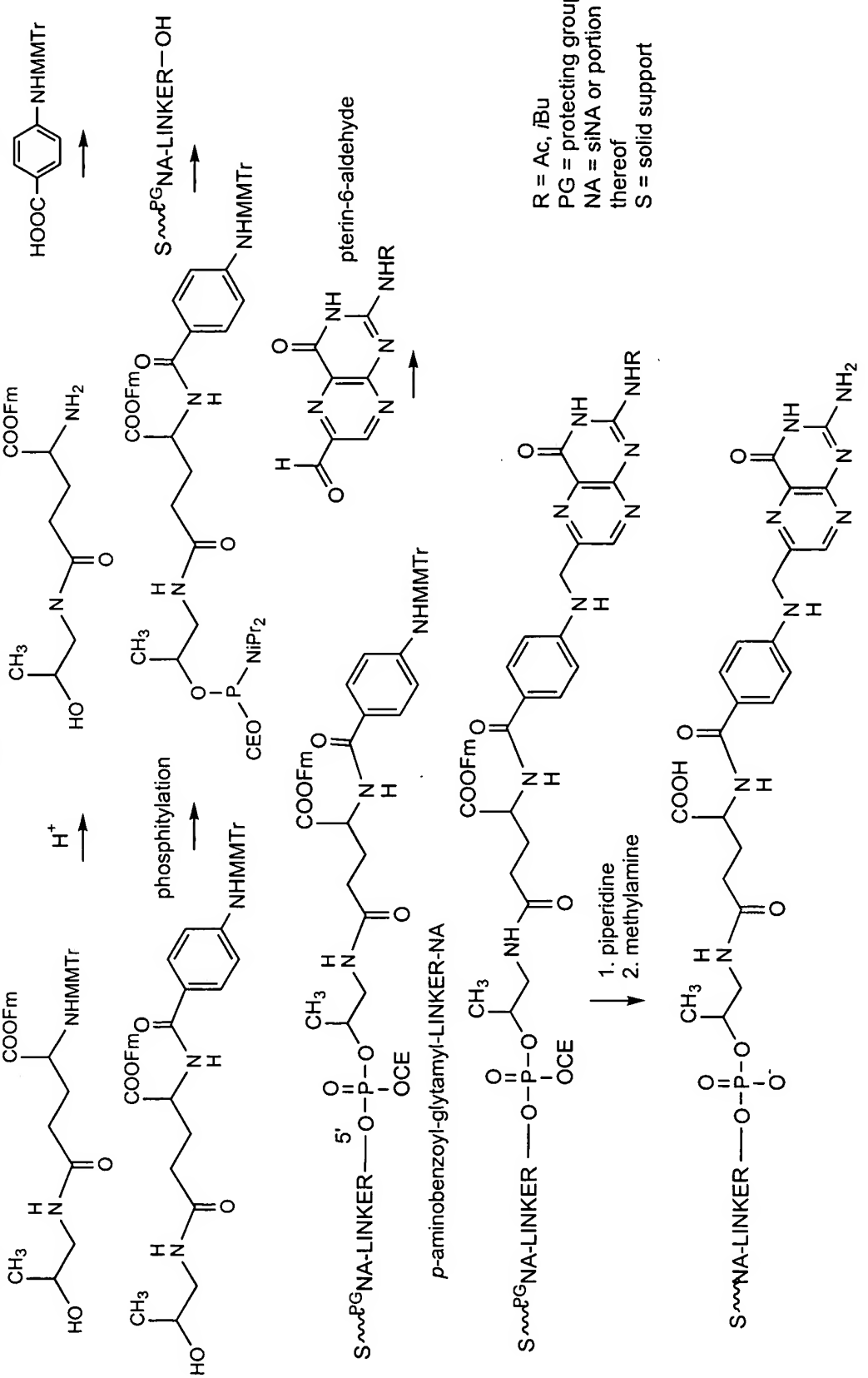

NA = siNA or a portion thereof
p = phosphorous moiety

**Figure 44**

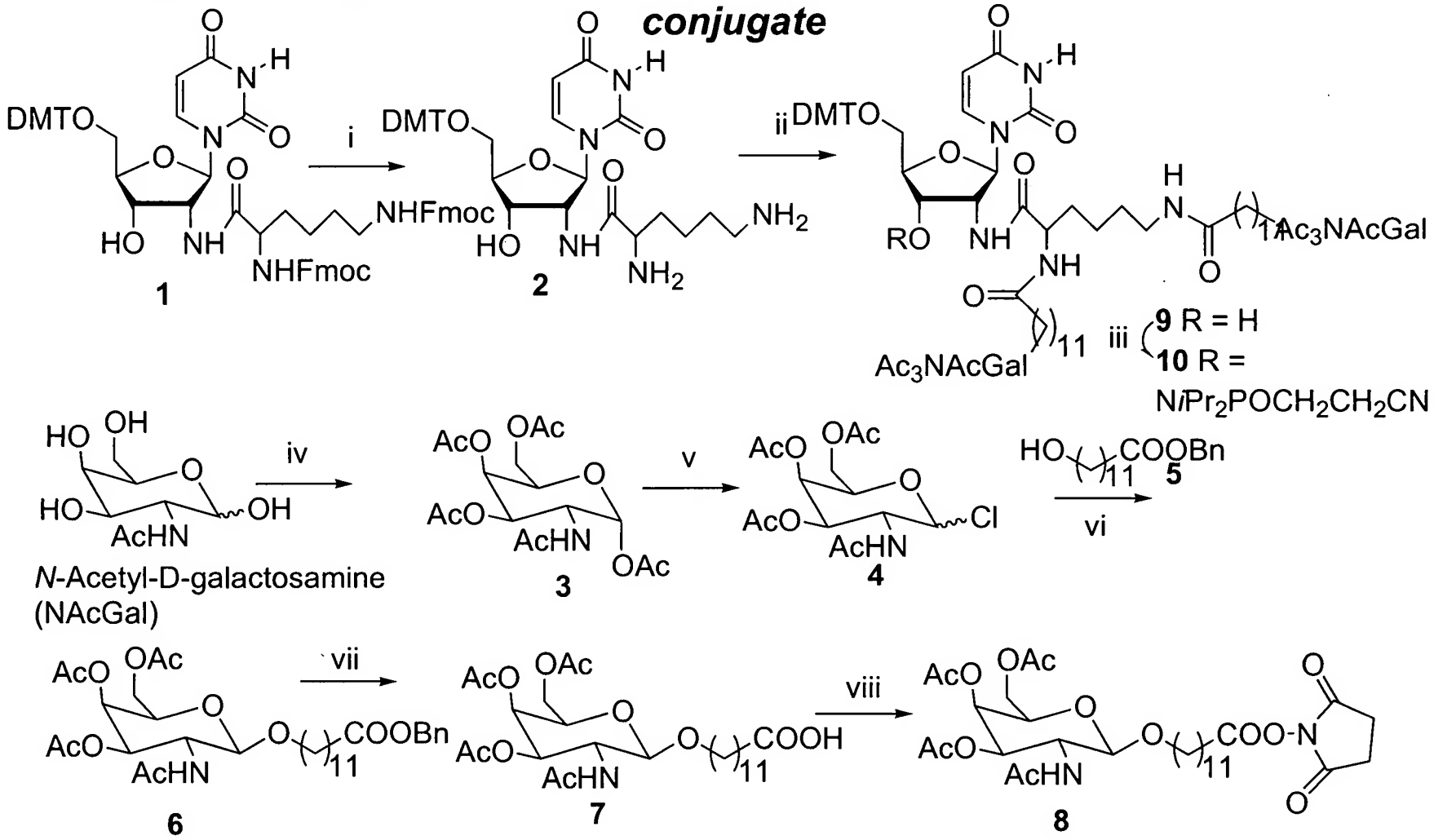



NA = siNA or a portion thereof
p = phosphorous moiety

**Figure 45: Solid Phase Post-synthetic conjugation of pteroic acid**

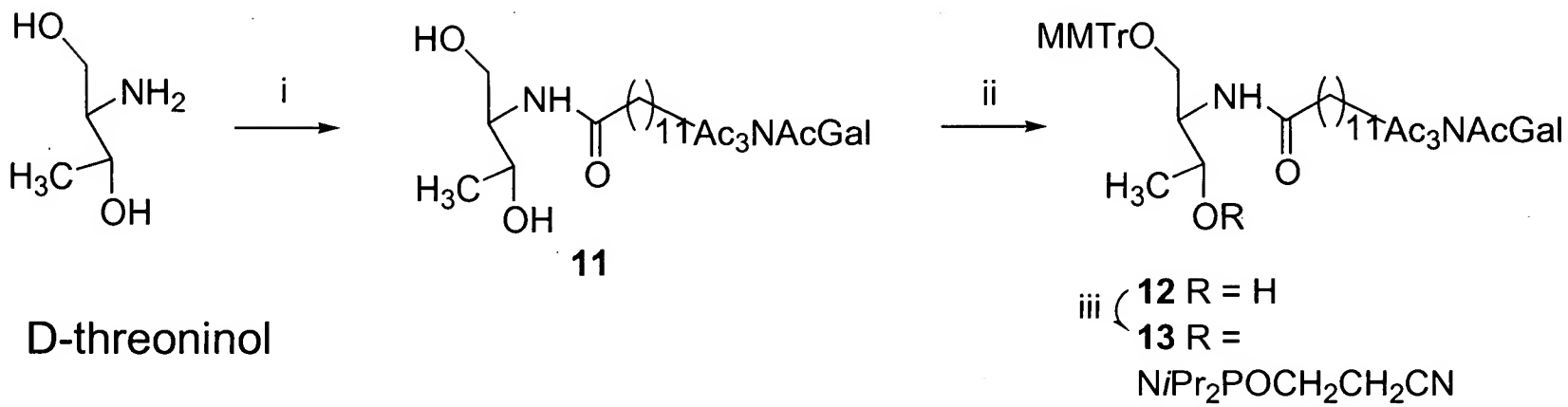


## *Figure 46: Synthesis of N-acetyl-D-galactosamine-2'-aminouridine conjugate*




Reagents and Conditions: (i) diethylamine, DMF, (ii) **8**, diisopropylethylamine, DMF, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, $CH_2Cl_2$, (iv) $Ac_2O$, TEA, $CH_3CN$, (v) HCl, $Ac_2O$, (vi) $Hg(CN)_2$, MS 4A, $CH_3NO_2$-toluene 1:1, (vii) $H_2$, 5% Pd-C, ethanol, (viii) *N*-hydroxysuccinimide, DCC, THF.

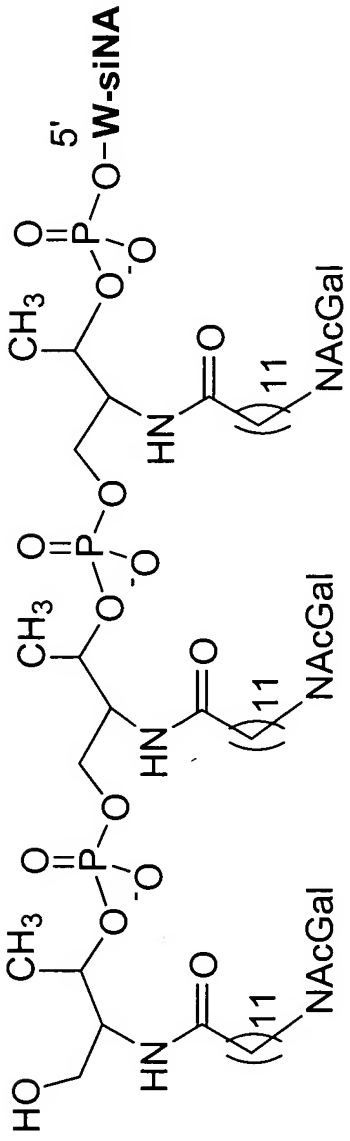
## *Figure 47: Synthesis of N-acetyl-D-galactosamine-D-threoninol conjugate*




D-threoninol

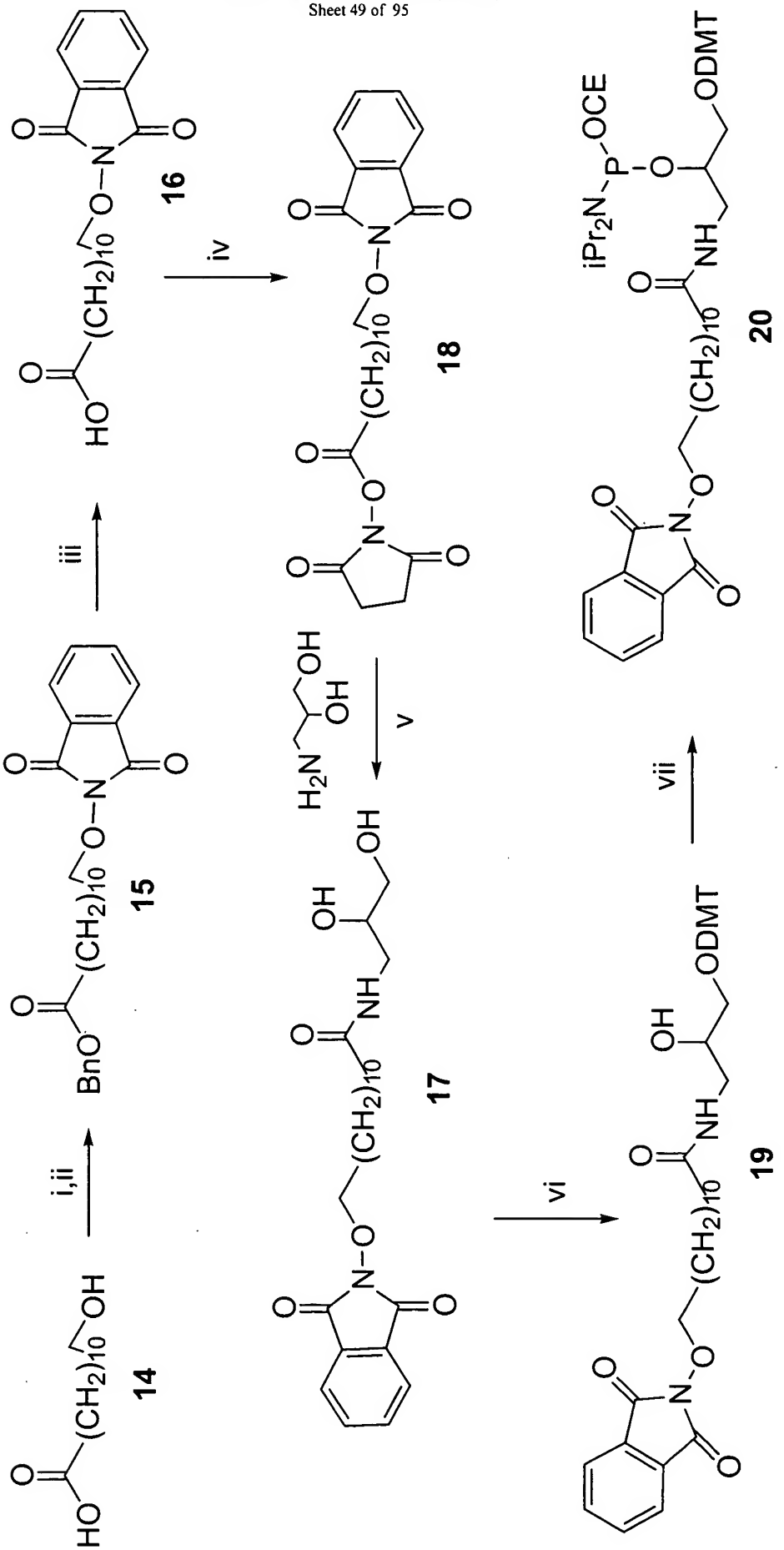
Reagents and Conditions: (i) **7**, DCC, *N*-hydroxysuccinimide, (ii) MMTr-Cl, pyridine, (iii) 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, 1-methylimidazole, DIPEA, $CH_2Cl_2$.

***Figure 48: Conjugation of targeting ligands to the 5'-end of a siNA molecule***

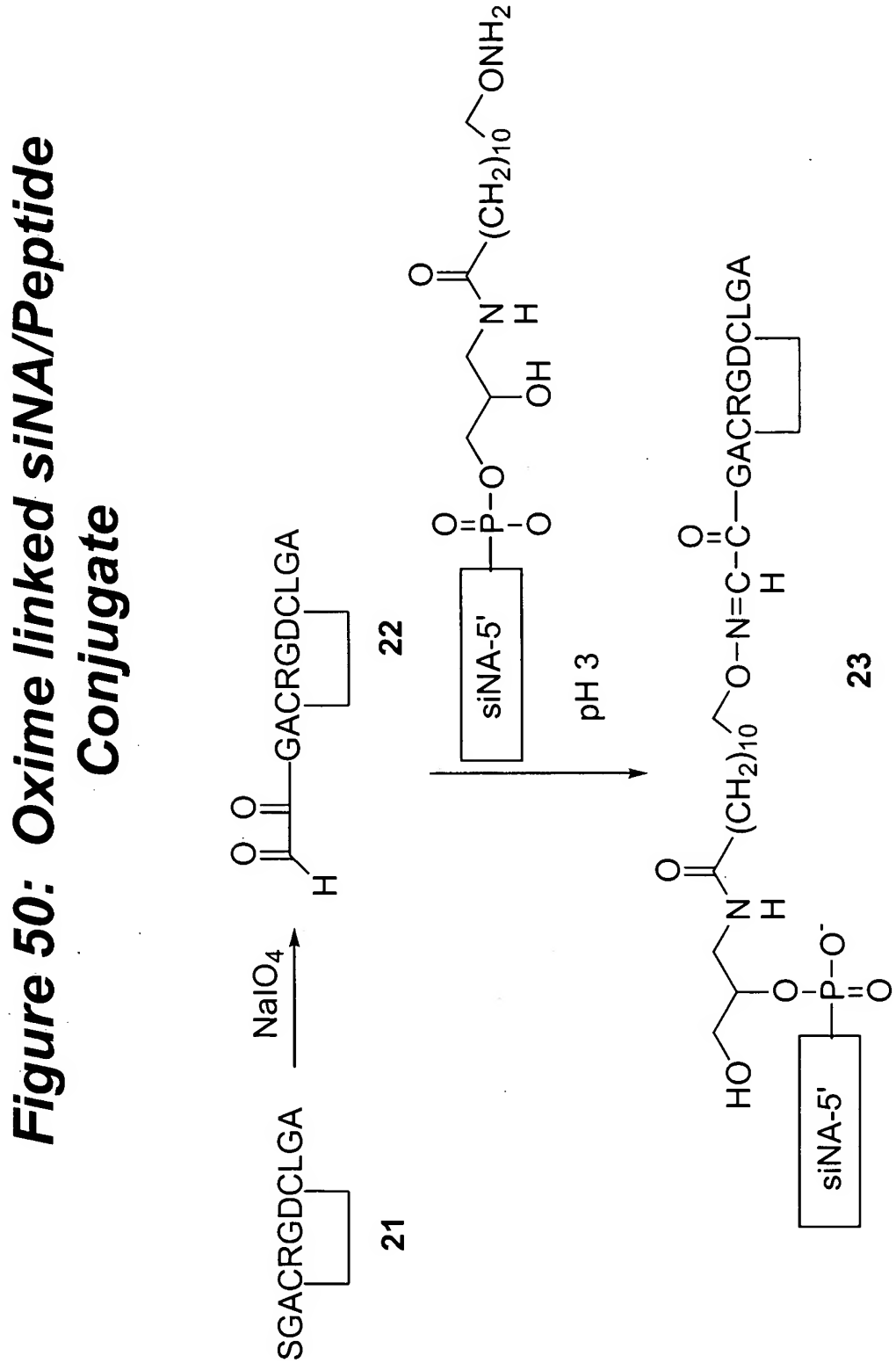



*N*-acetyl-D-galactosamine conjugate

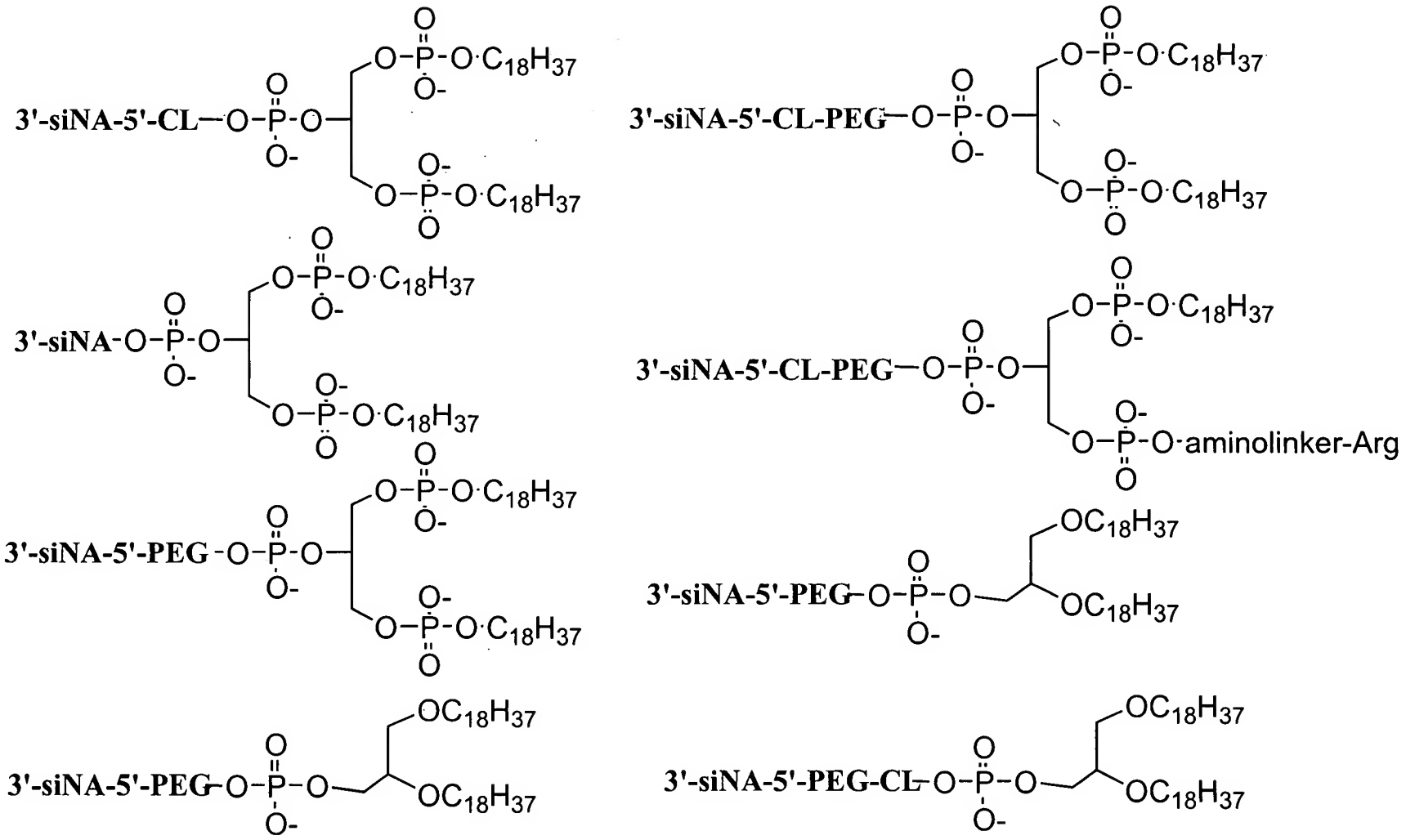
**Figure 49: Synthesis of dodecanoic acid linker**



# Figure 50: Oxime linked siNA/Peptide Conjugate



# *Figure 51: siNA/Phospholipid Conjugates*




**PEG=polyethylene glycol**
**CL=cleavable linker (e.g. A-dT, C-dT)**
**siNA= short interfering nucleic acid molecule or a portion thereof**

# *Figure 52: siNA Phospholipid Conjugate*

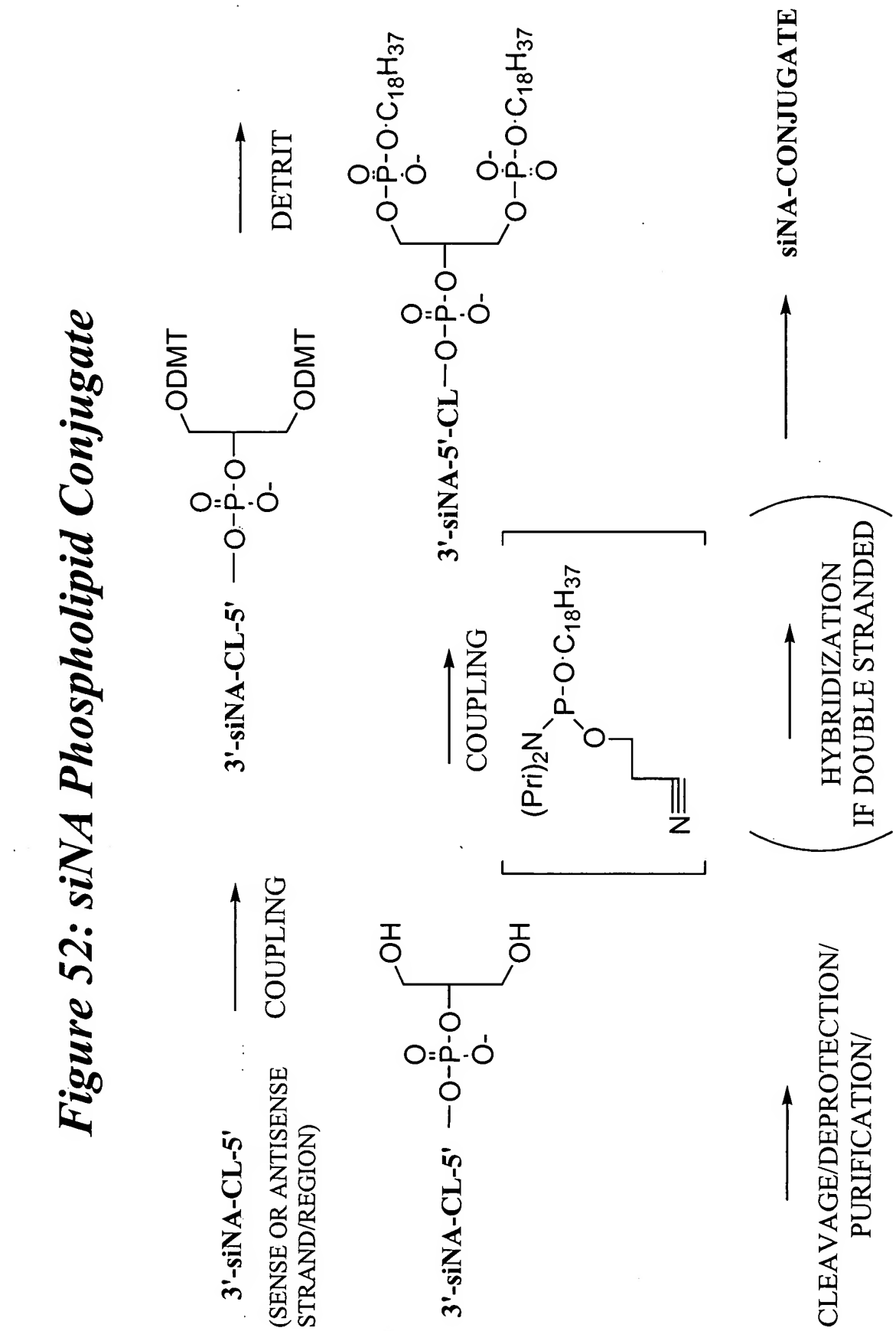
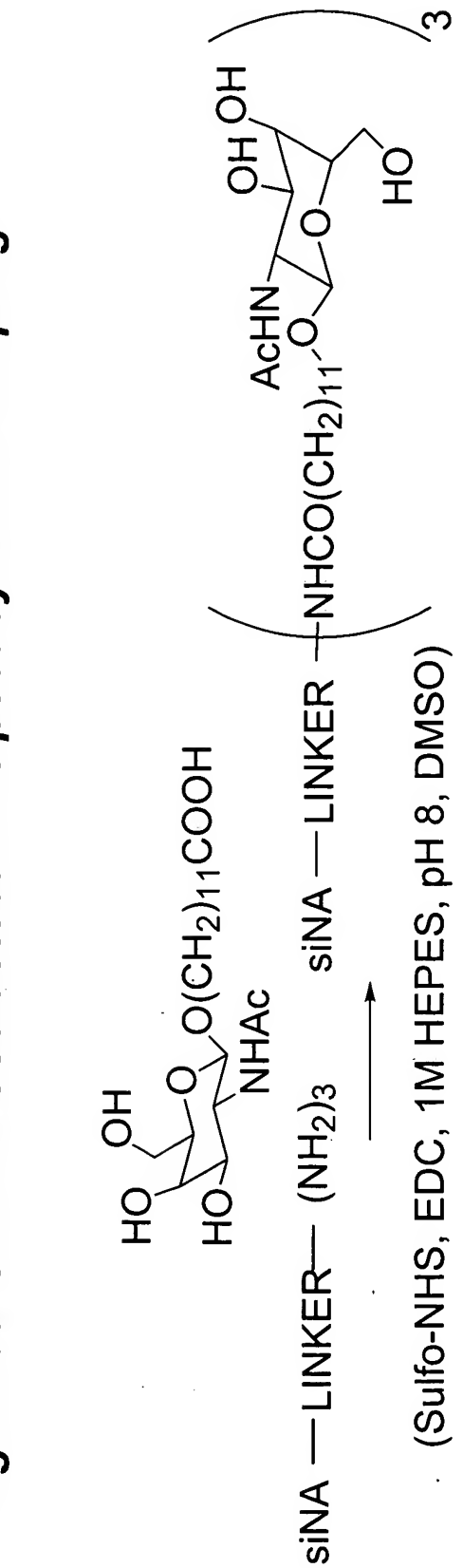


***Figure 53: siNA-NAcGalactosamine post-synthetic coupling***




FOR EXAMPLE: OLIGO-LINKER =




Where n is an integer from 1 to 20

# *Figure 54: siNA Cholesterol Conjugate*

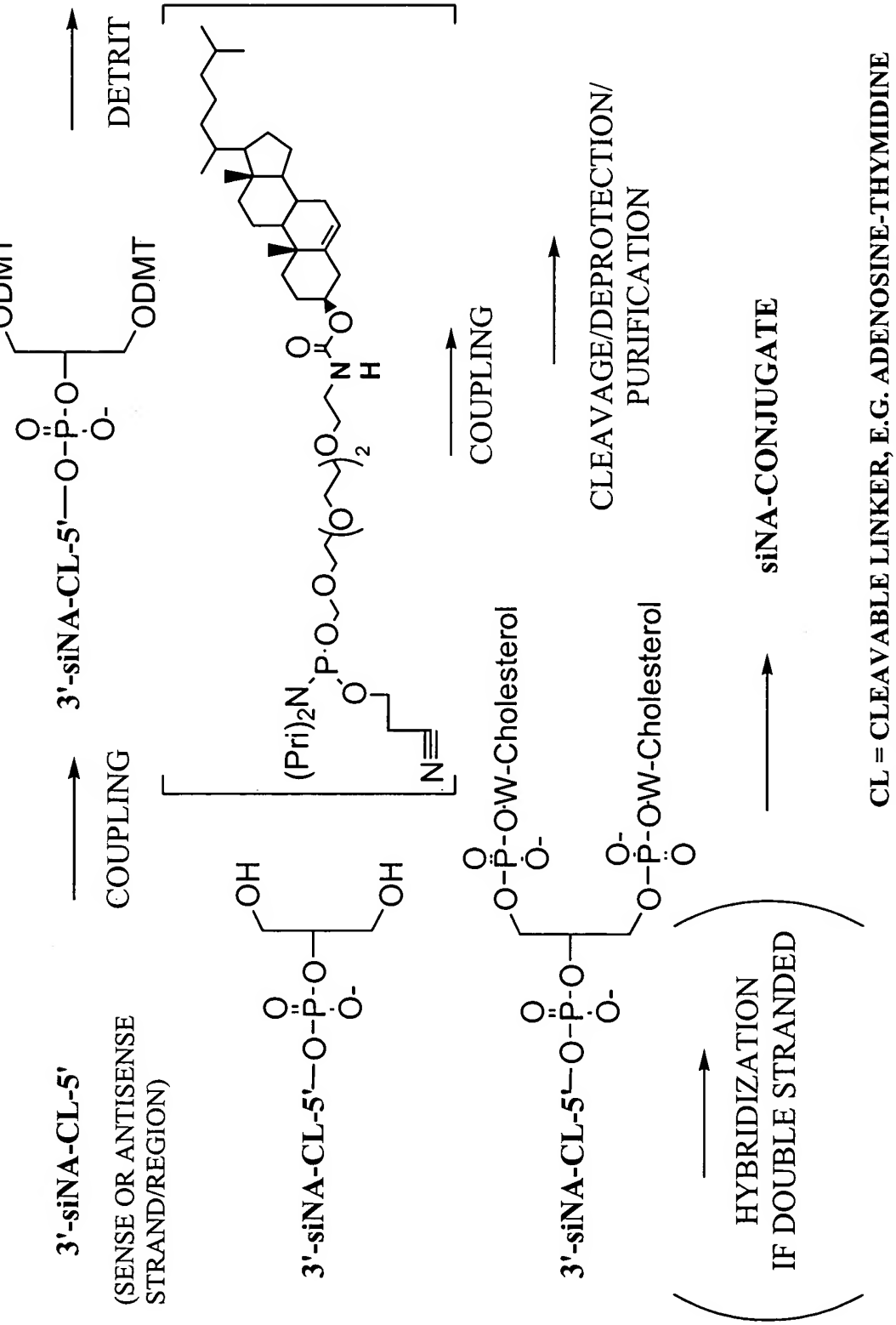
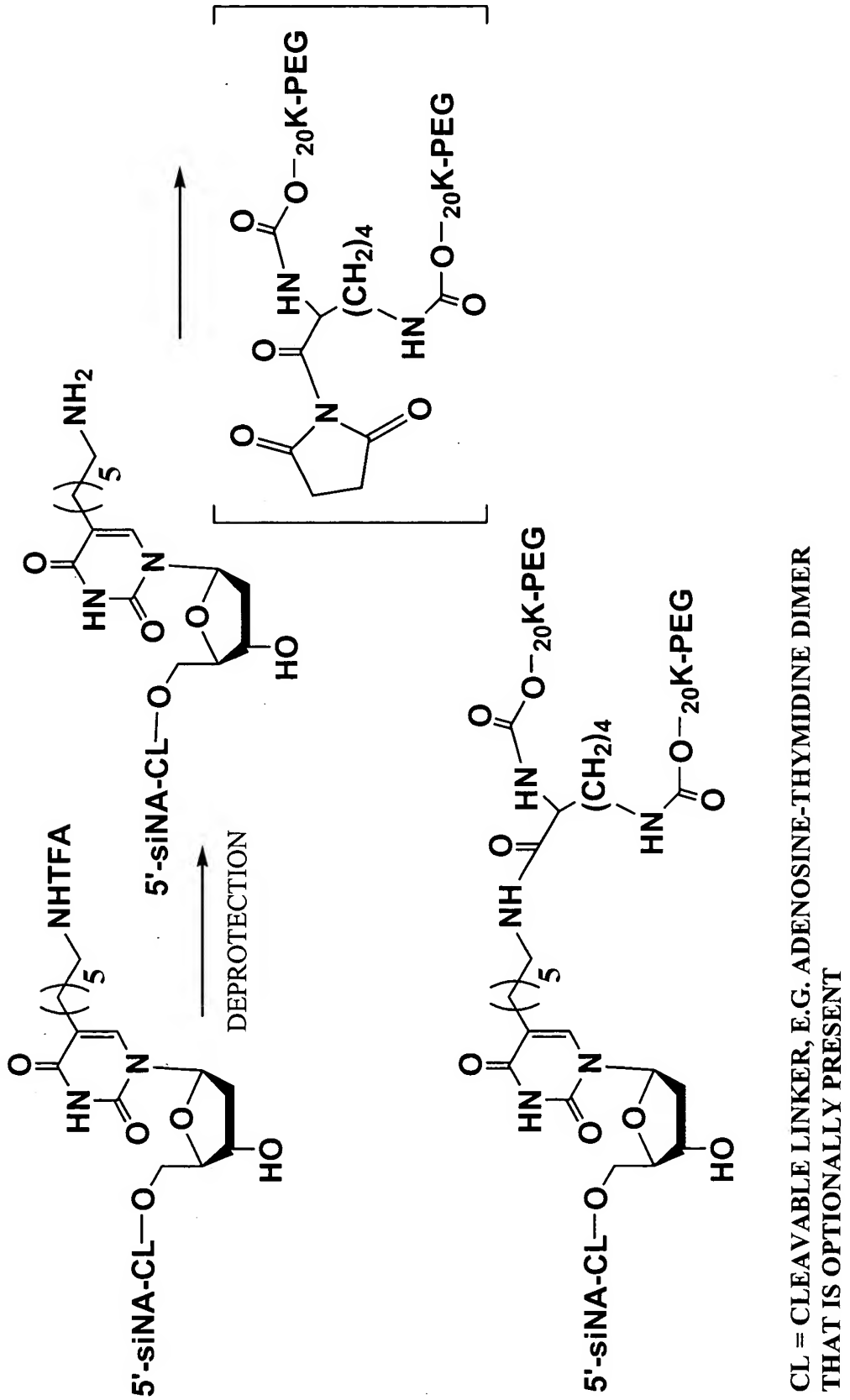
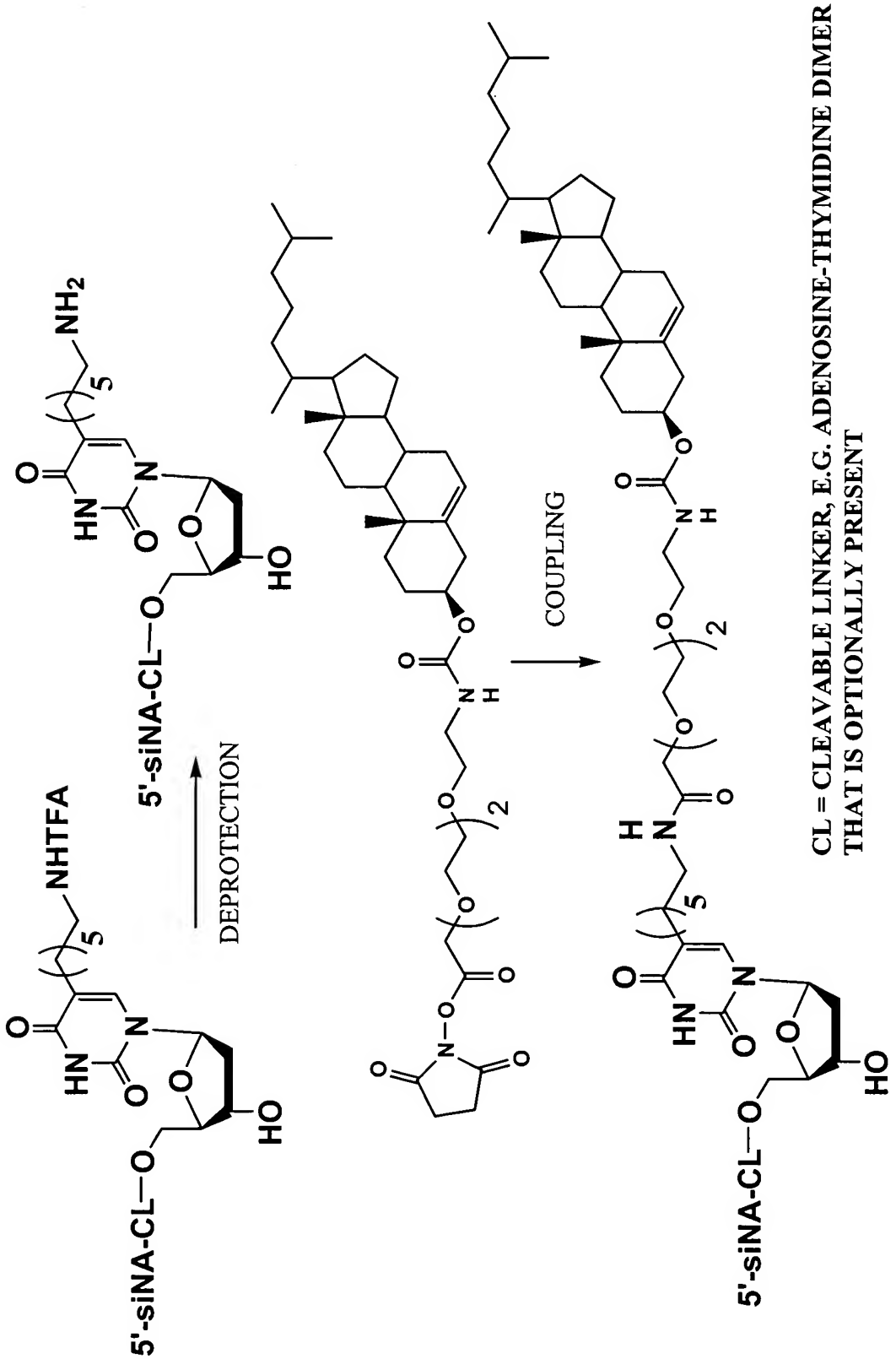


*Figure 55: siNA 3'-PEG Conjugate*



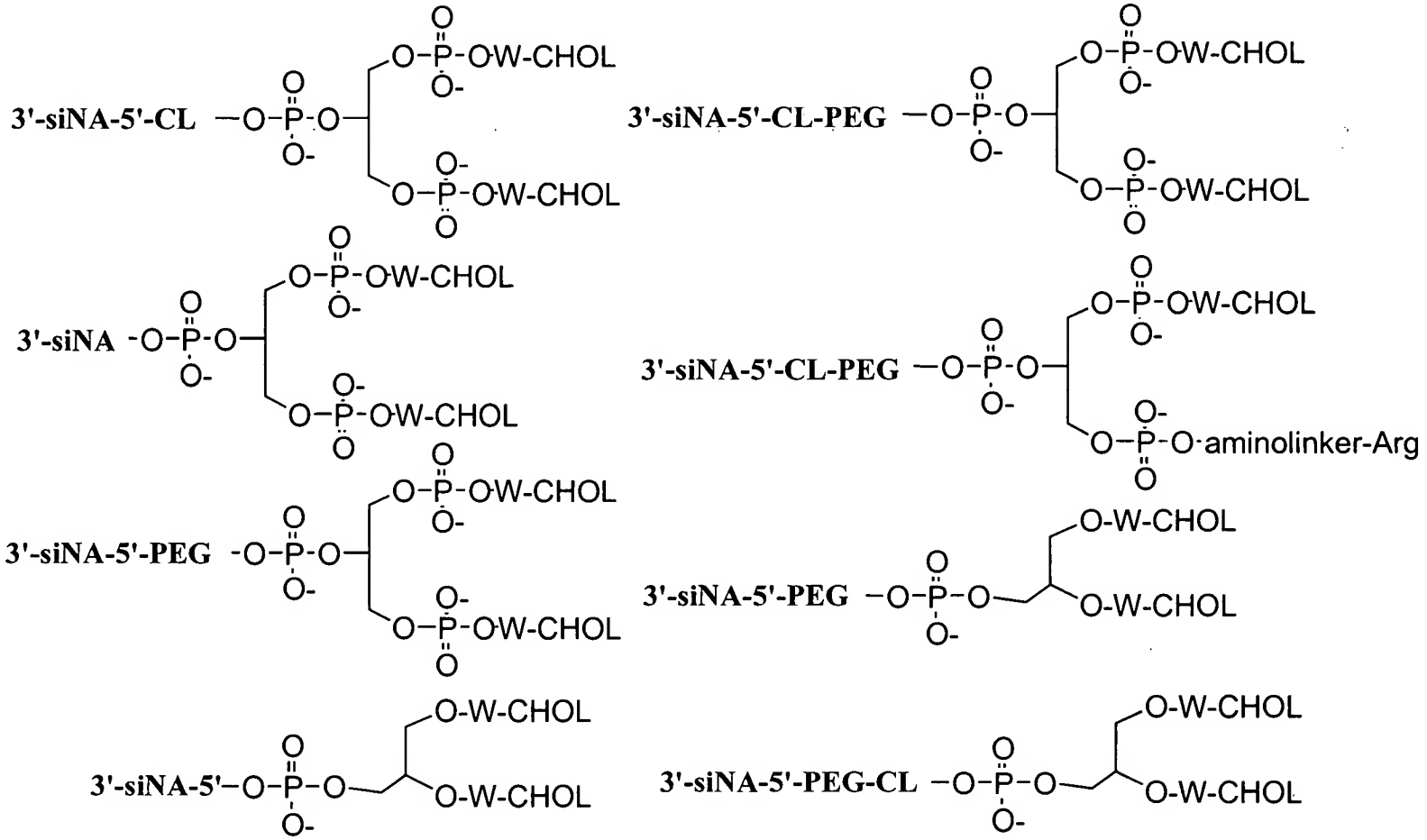

CL = CLEAVABLE LINKER, E.G. ADENOSINE-THYMIDINE DIMER THAT IS OPTIONALLY PRESENT

*Figure 56: siNA 3'-Cholesterol Conjugate*



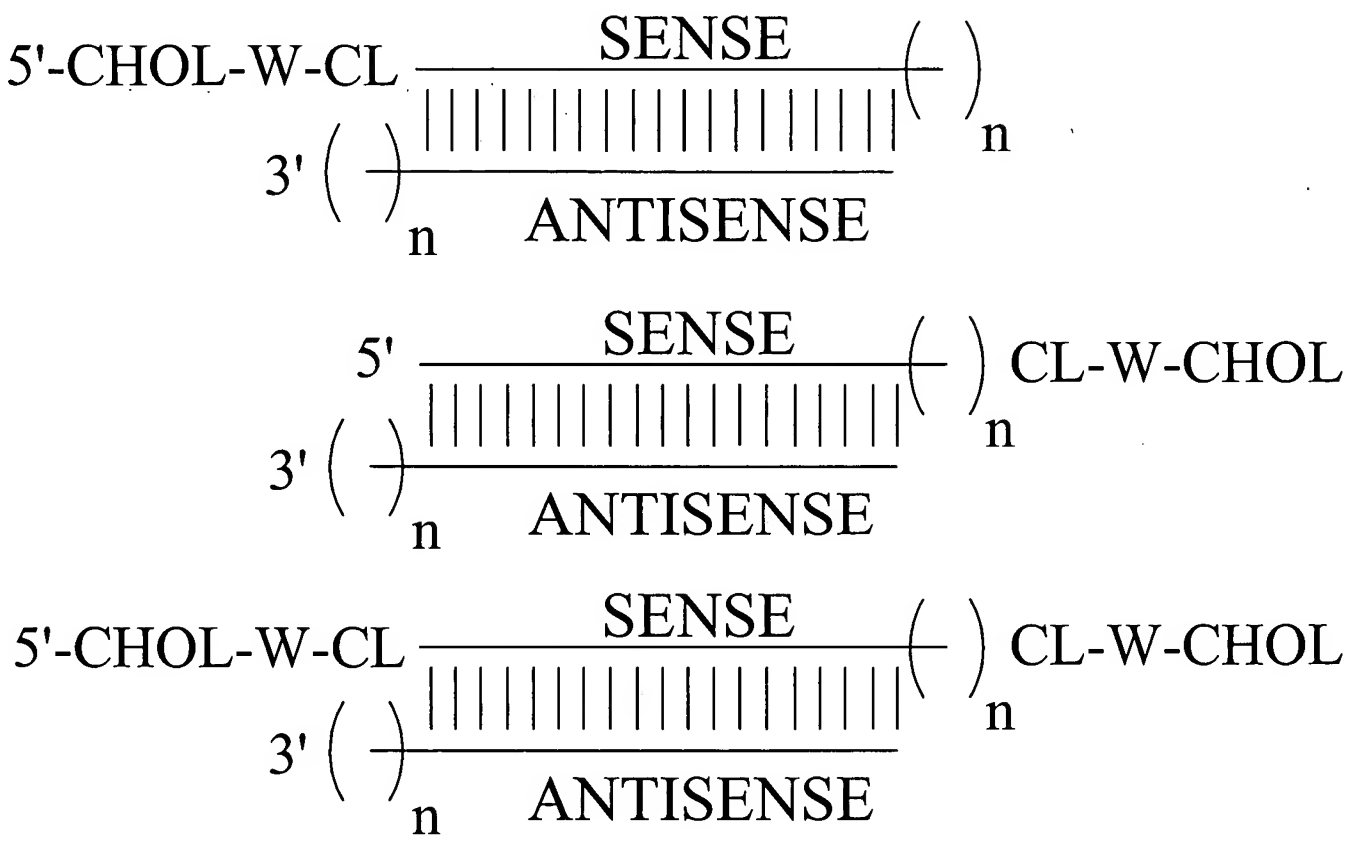

CL = CLEAVABLE LINKER, E.G. ADENOSINE-THYMIDINE DIMER THAT IS OPTIONALLY PRESENT

# *Figure 57: Nucleic Acid Cholesterol Conjugates*



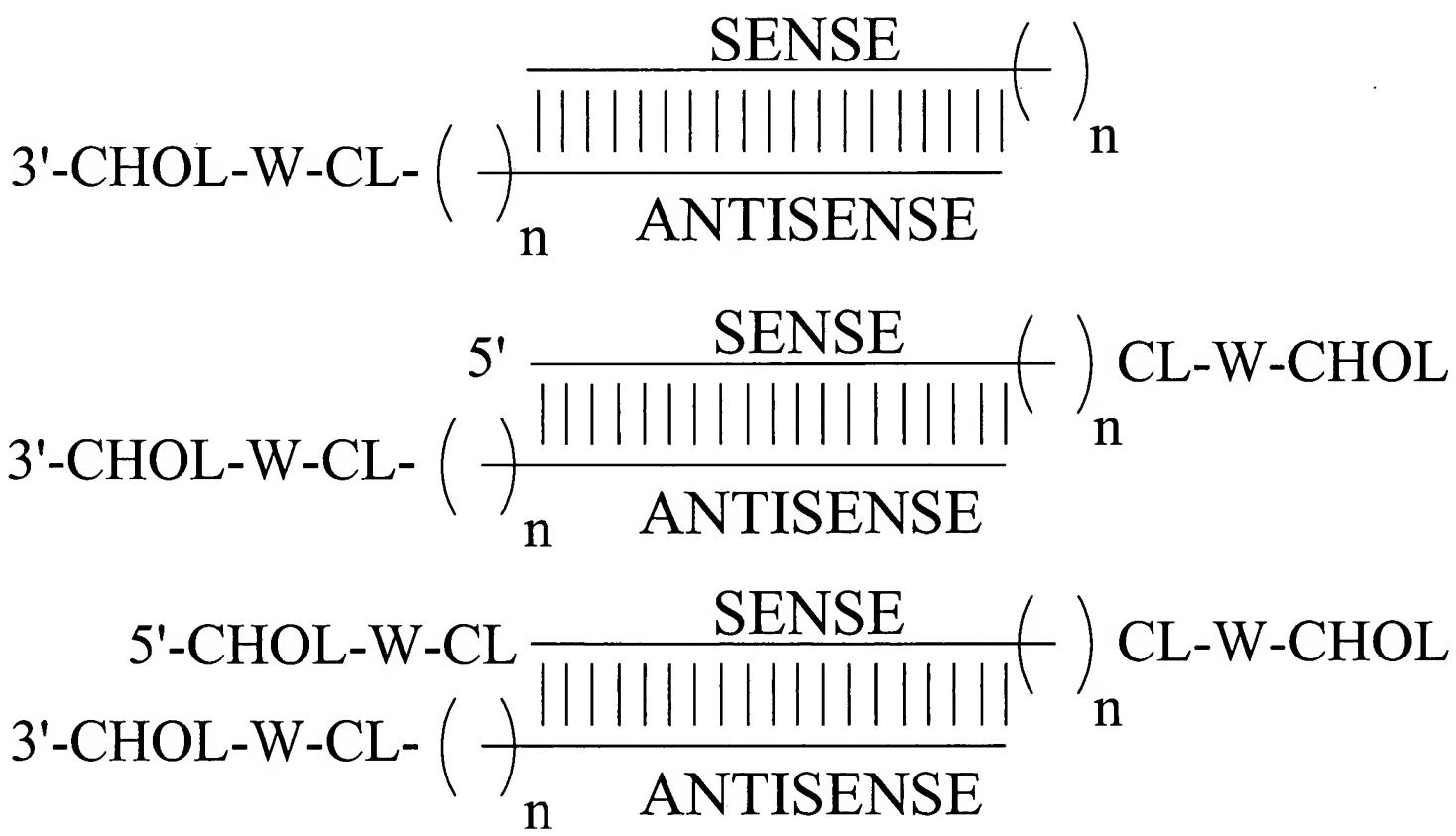

**PEG=polyethylene glycol**
**CL=cleavable linker (e.g. A-dT, C-dT)**
**siNA= short interfering nucleic acid molecule or a portion thereof**
**CHOL=cholesterol or an analog or metabolite thereof**
**W= linker molecule (see for example Formulae 109 or 112)**

# *Figure 58: siNA Cholesterol Conjugates*



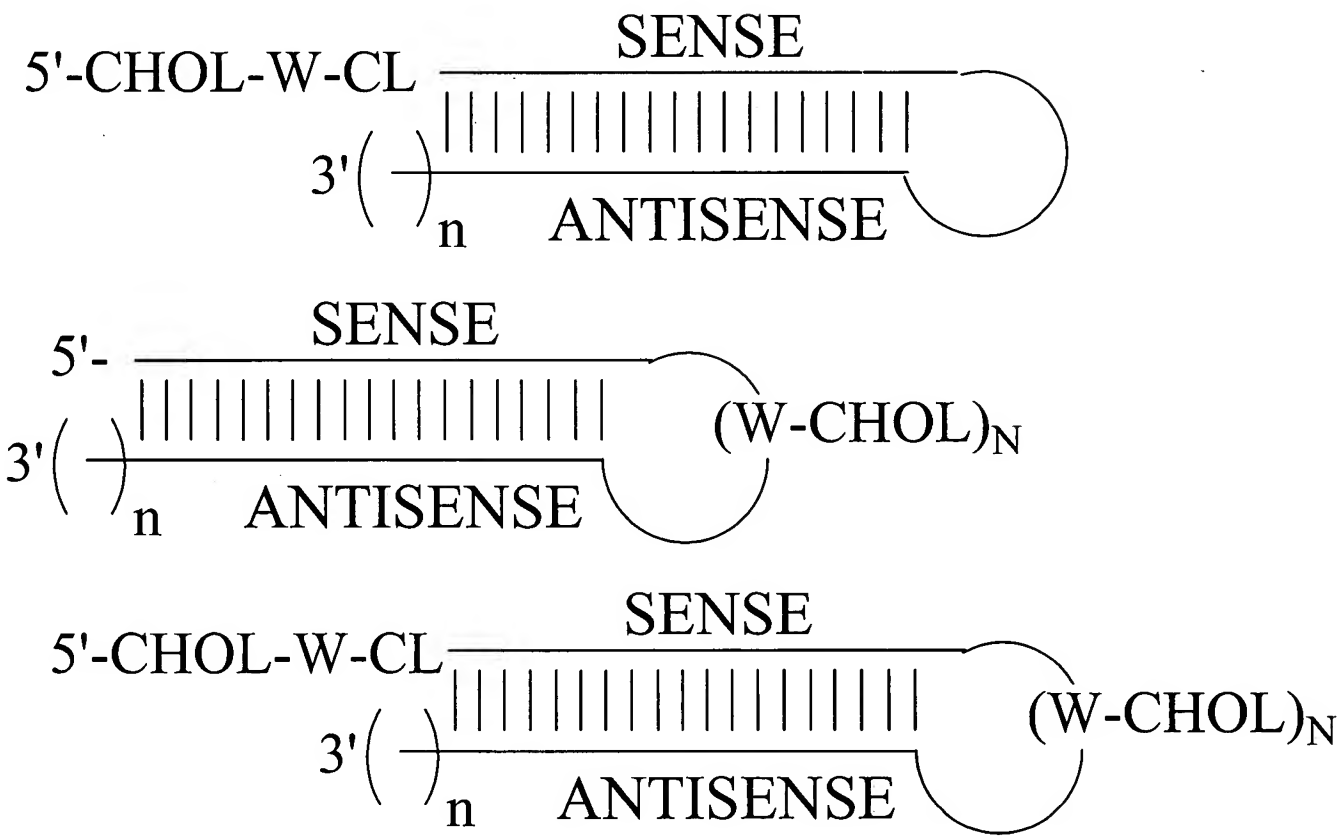

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**CHOL=cholesterol or an analog or metabolite thereof**
**W= linker molecule (see for example Formulae 107, 108, 109 or 115)**
**n = integer, e.g. 1, 2, or 3**

# *Figure 59: siNA Cholesterol Conjugates*



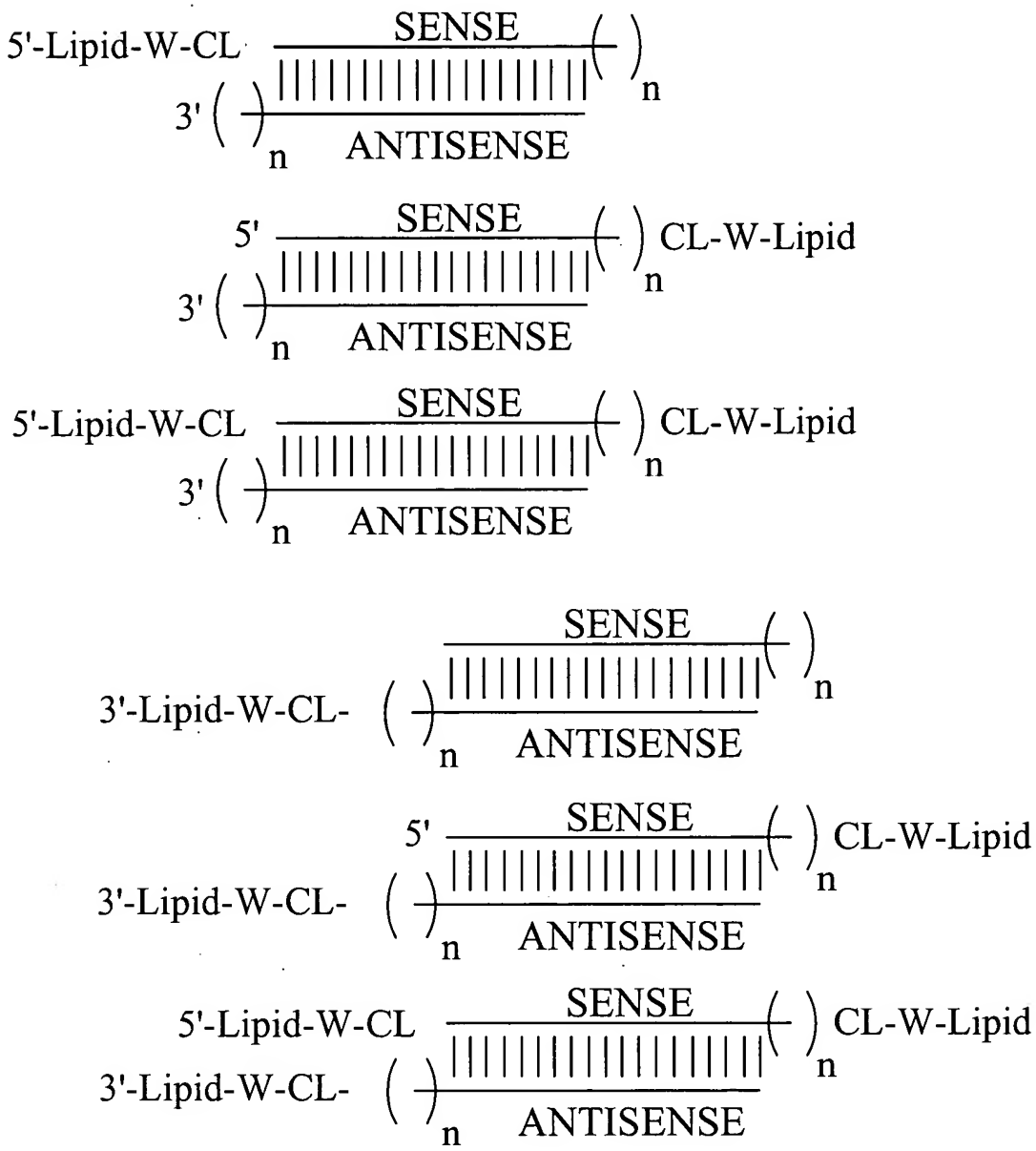

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**CHOL=cholesterol or an analog or metabolite thereof**
**W= linker molecule (see for example Formulae 107, 108, 109 or 115)**
**n = integer, e.g. 1, 2, or 3**

# *Figure 60: siNA Cholesterol Conjugates*



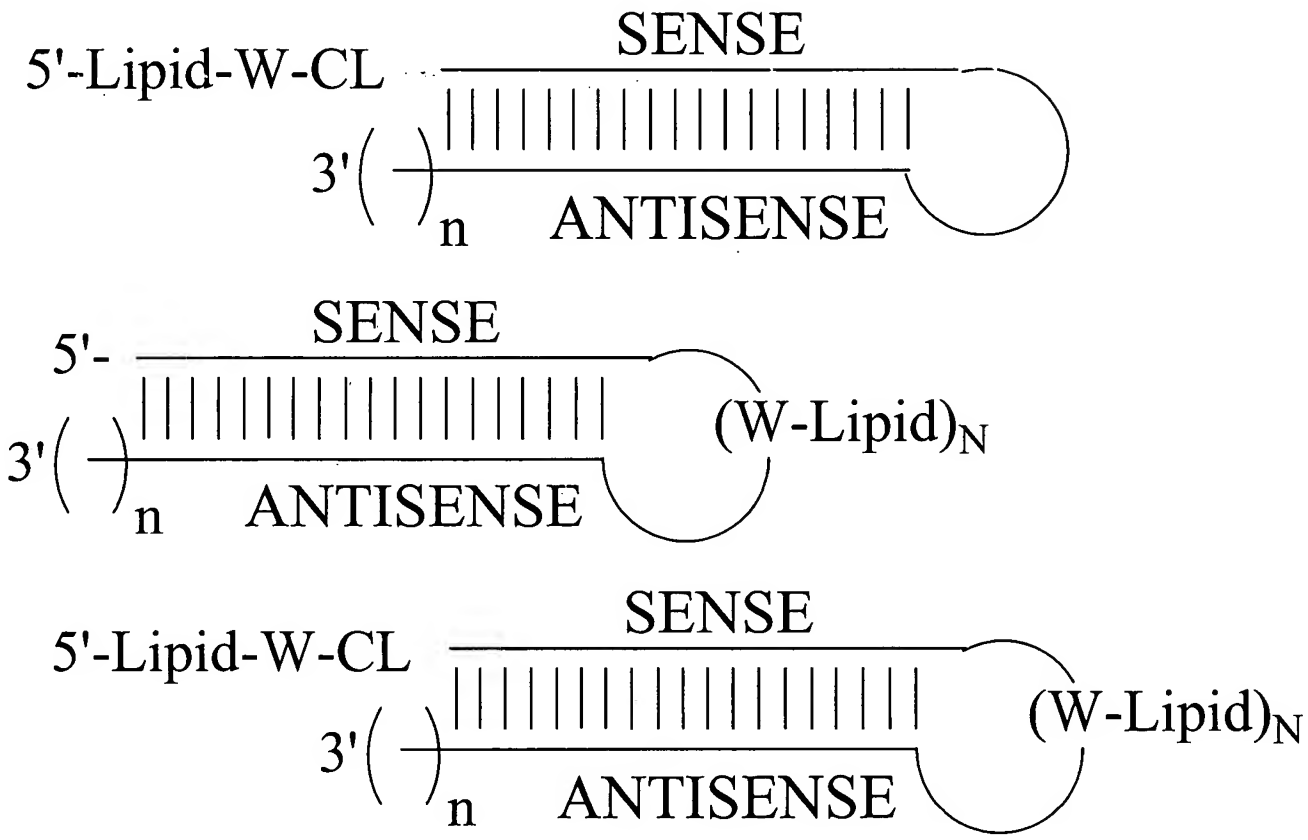

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**CHOL=cholesterol or an analog or metabolite thereof**
**W= linker molecule (see for example Formulae 107, 108, 109 or 112)**
**n = integer, e.g. 1, 2, or 3**
**N=integer, e.g. 1, 2, 3, or 4**

# *Figure 61: siNA Lipid Conjugates*



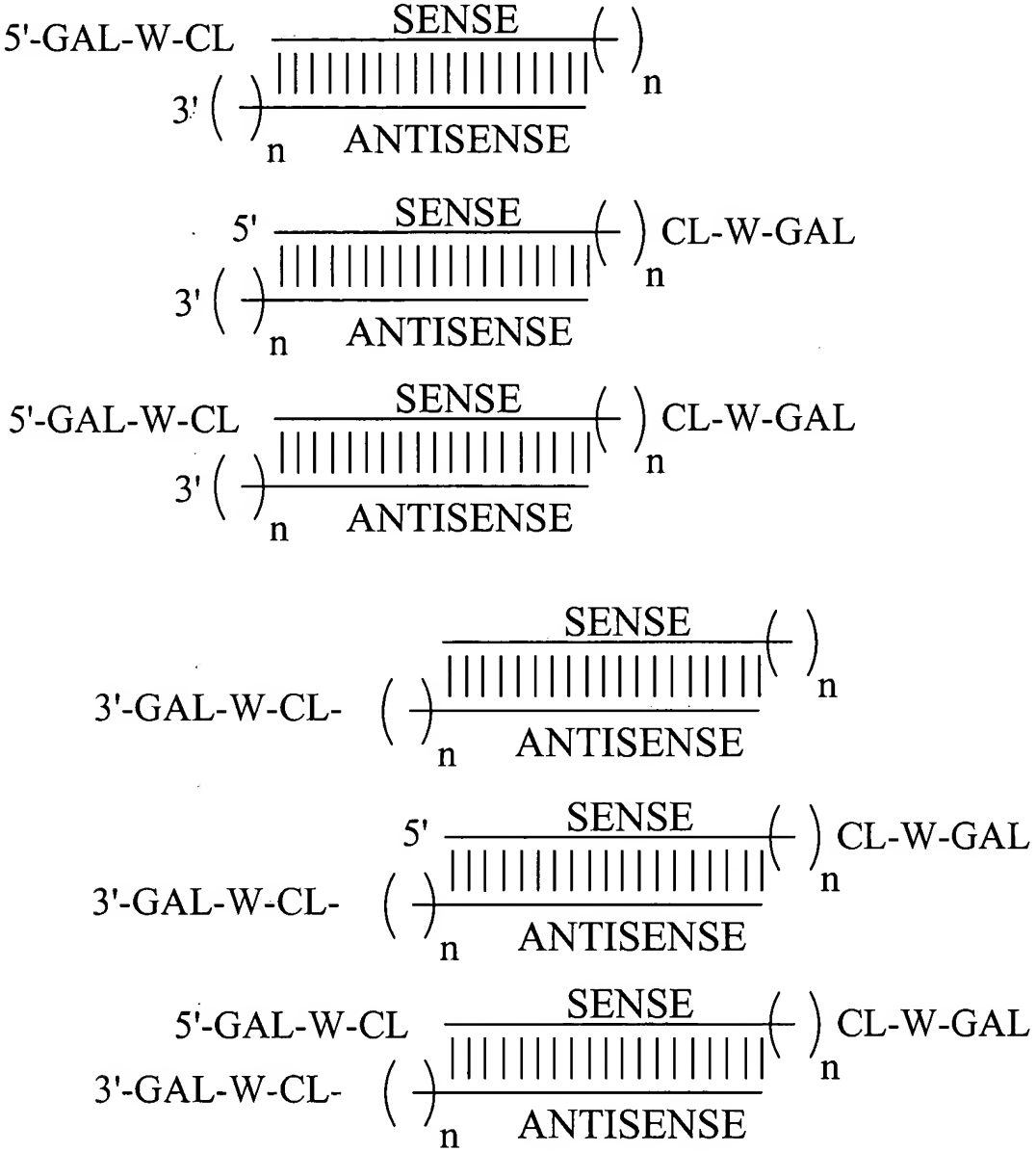

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**Lipid=Straight chain or branched alkyl or fatty acid, e.g. $C_{18}H_{37}$**
**W= linker molecule (see for example Formulae 48, 49, 64, or 65)**
**n = integer, e.g. 1, 2, or 3**

# *Figure 62: siNA Lipid Conjugates*



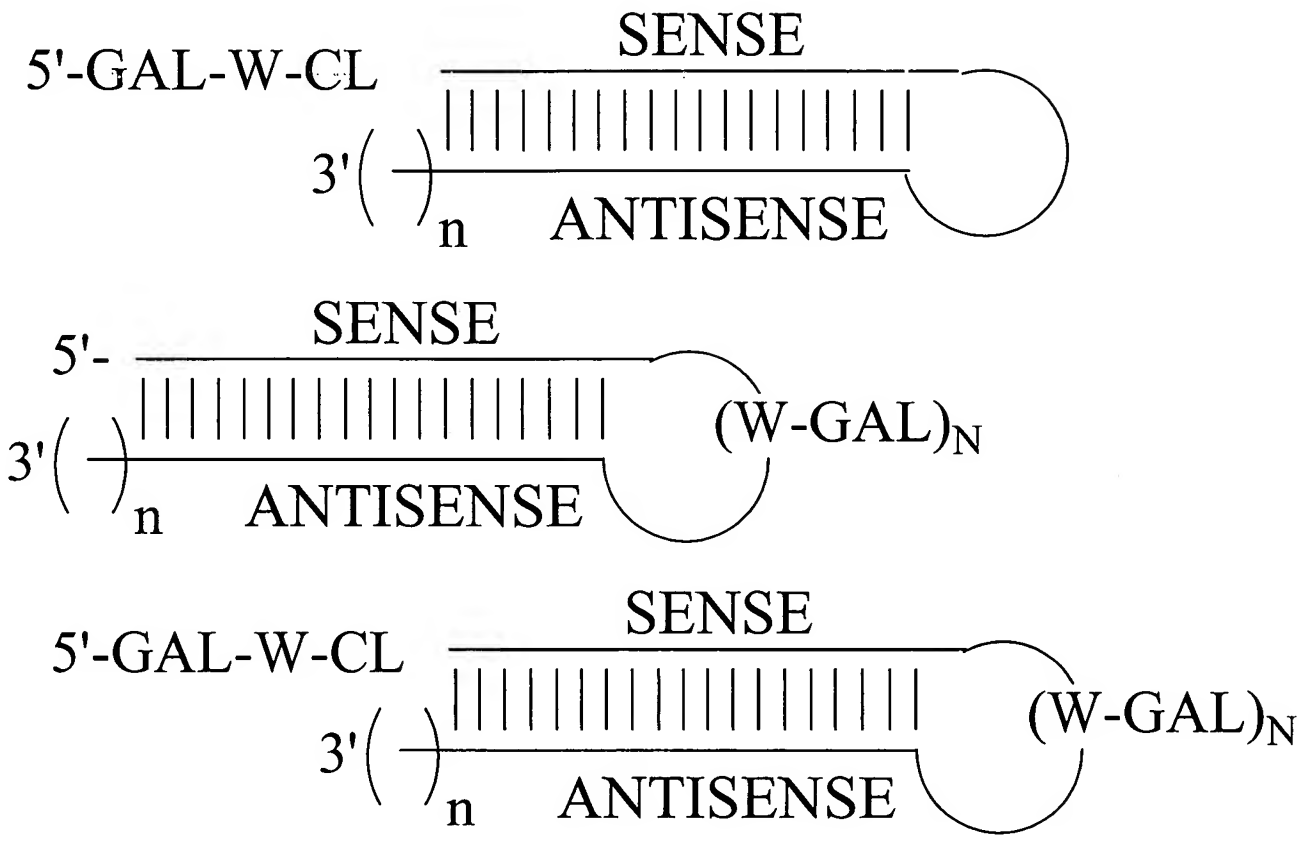

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**Lipid=Straight chain or branched alkyl or fatty acid, e.g. $C_{18}H_{37}$**
**W= linker molecule (see for example Formulae 48, 49, 64, or 65)**
**n = integer, e.g. 1, 2, or 3**
**N=integer, e.g. 1, 2, 3, or 4**

# *Figure 63: siNA Galactosamine Conjugates*



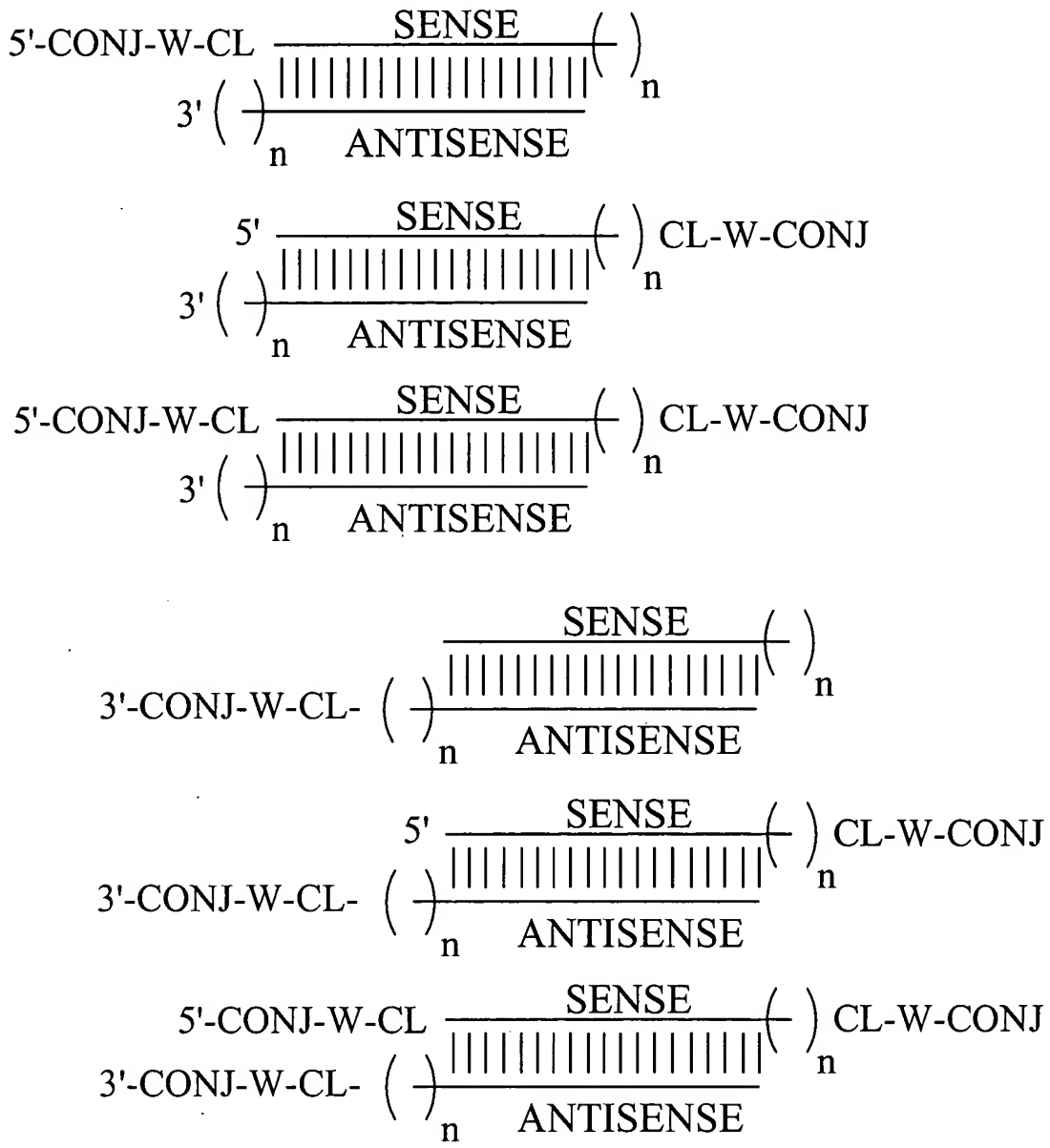

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106**
**W= linker molecule (see for example Formulae 102 or 103)**
**n = integer, e.g. 1, 2, or 3**

# *Figure 64: siNA Galactosamine Conjugates*



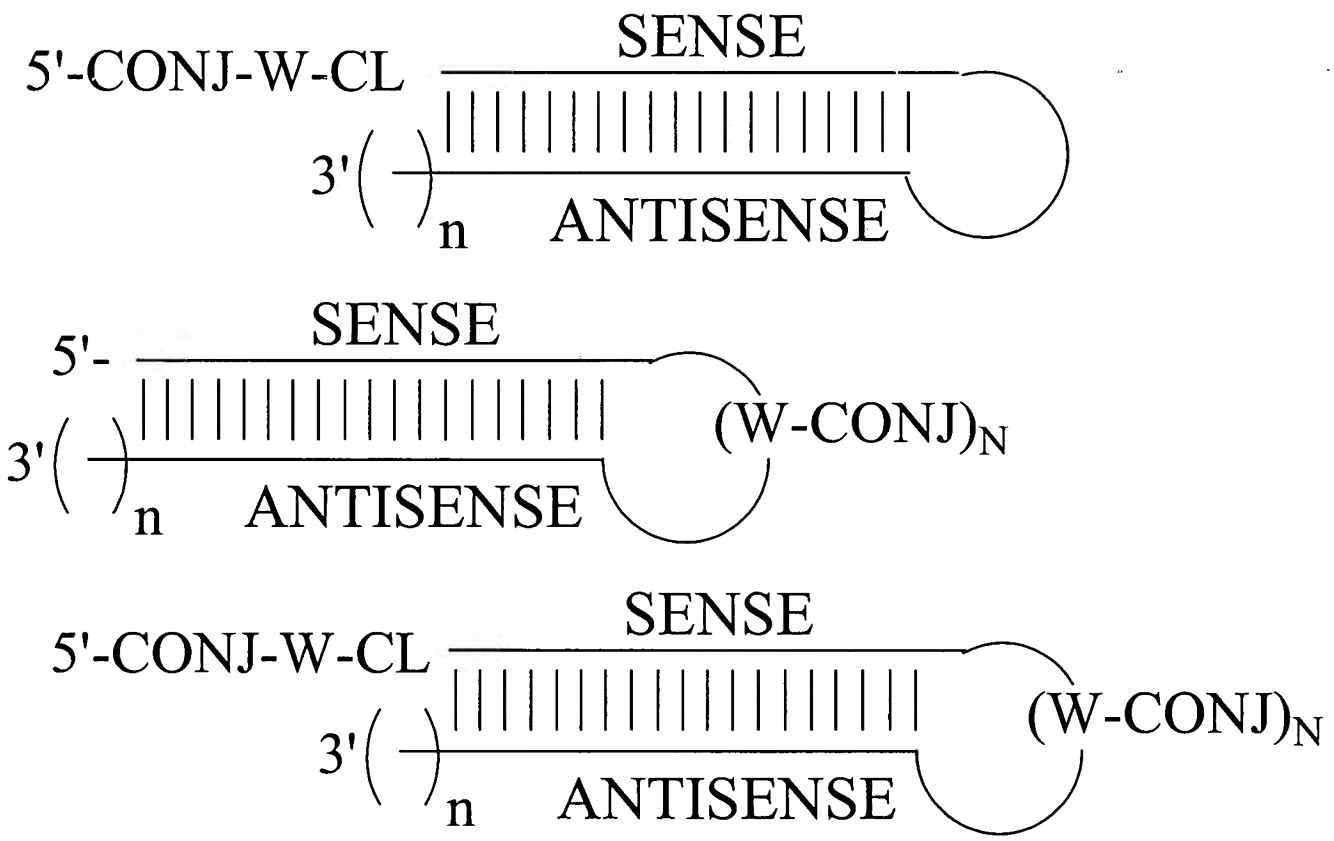

**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**GAL=GALACTOSAMINE; e.g. compounds having Formulae 51-56, 86, 92, 99, 100, 103, 105, 106**
**W= linker molecule (see for example Formulae 102 or 103)**
**n = integer, e.g. 1, 2, or 3**
**N=integer, e.g. 1, 2, 3, or 4**

# *Figure 65: Generalized siNA Conjugate Design*




**CONJ=any biologically active molecule or conjugate as described herein**
**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**W= linker molecule**
**n = integer, e.g. 1, 2, or 3**

# *Figure 66: Generalized siNA Conjugate design*




**CONJ=any biologically active molecule or conjugate as described herein**
**CL=cleavable linker (e.g. A-dT, C-dT) that is optionally present**
**W= linker molecule**
**n = integer, e.g. 1, 2, or 3**
**N=integer, e.g. 1, 2, 3, or 4**

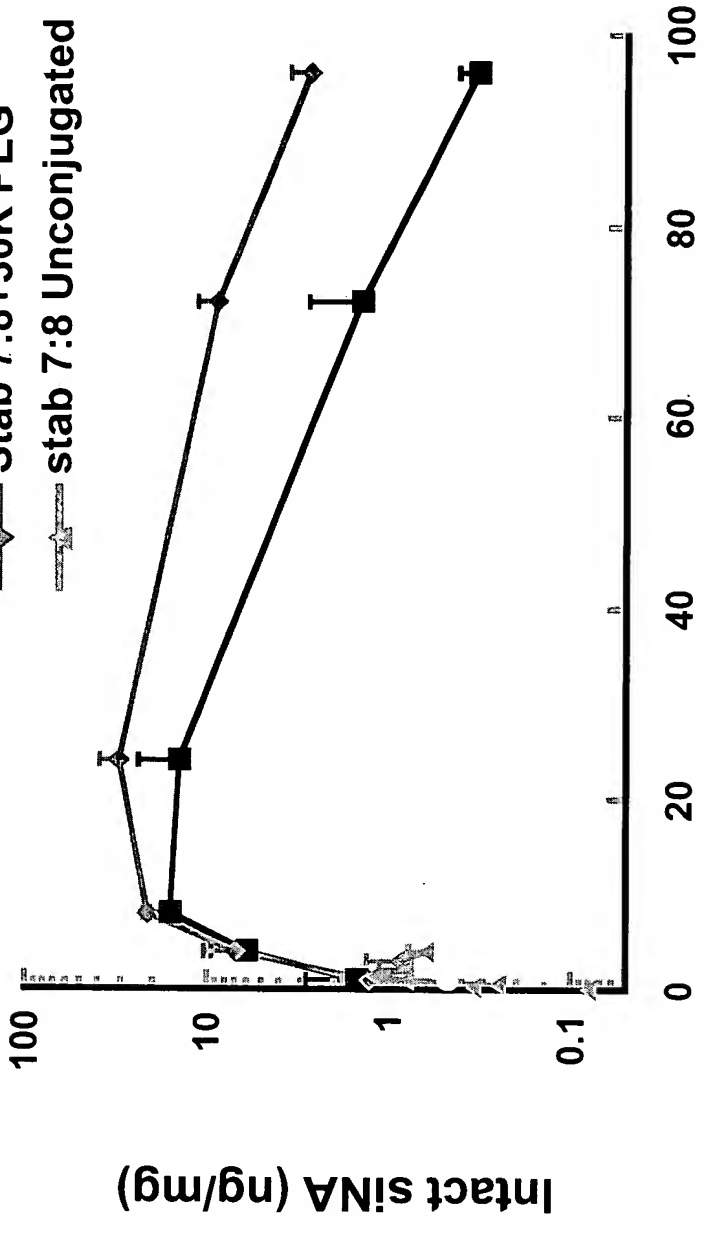



*Figure 67: Distribution of Intact siNA in Liver After SC Administration of Conjugated or Unconjugated Chemistries*

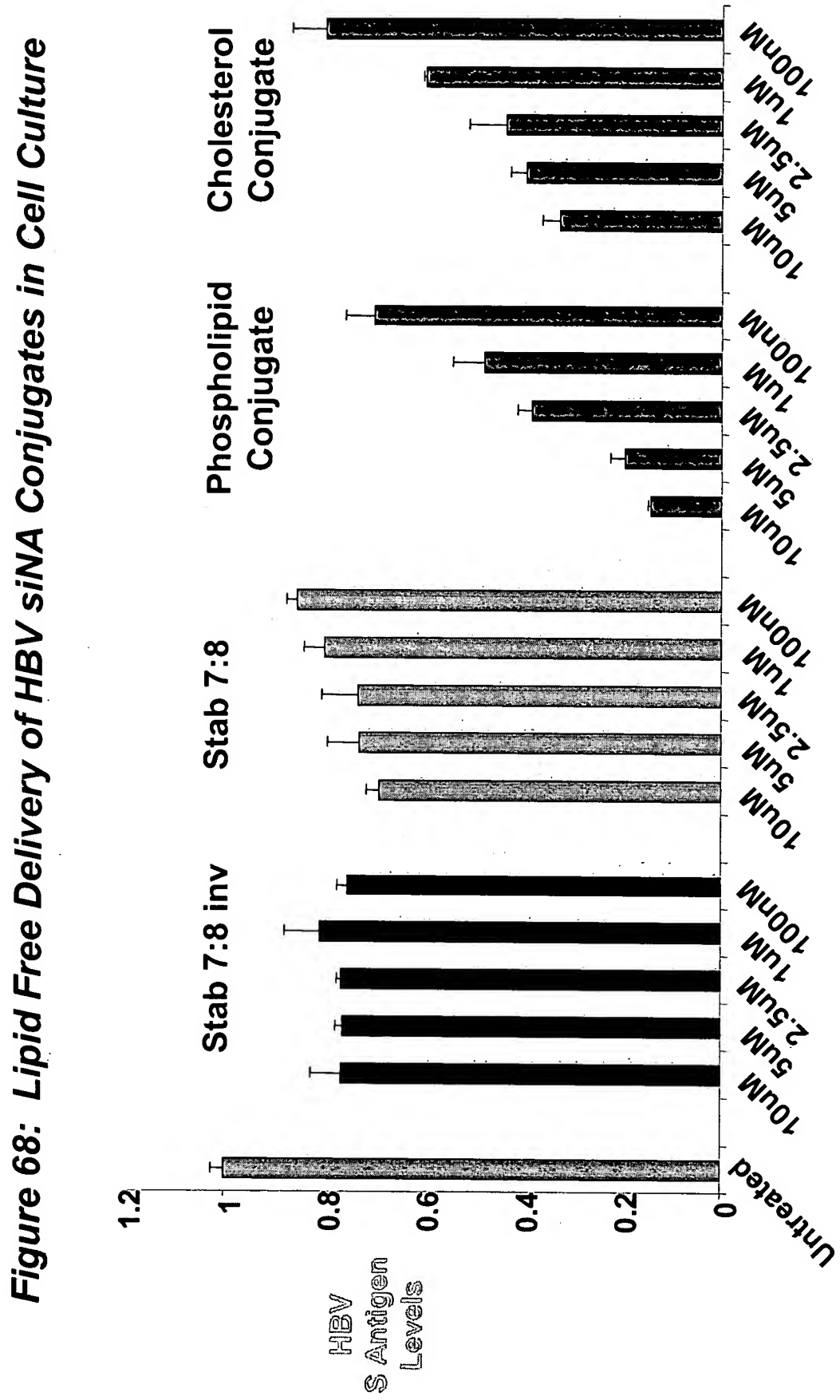


Figure 68: Lipid Free Delivery of HBV siNA Conjugates in Cell Culture
HBV S Antigen Levels
1.2
1
0.8
0.6
0.4
0.2
0
Untreated
10uM
5uM
2.5uM
1uM
100nM
Stab 7:8 inv
Stab 7:8
Phospholipid Conjugate
Cholesterol Conjugate

**Figure 69: Scale-up of "mono" Galactosamine phosphoramidite**

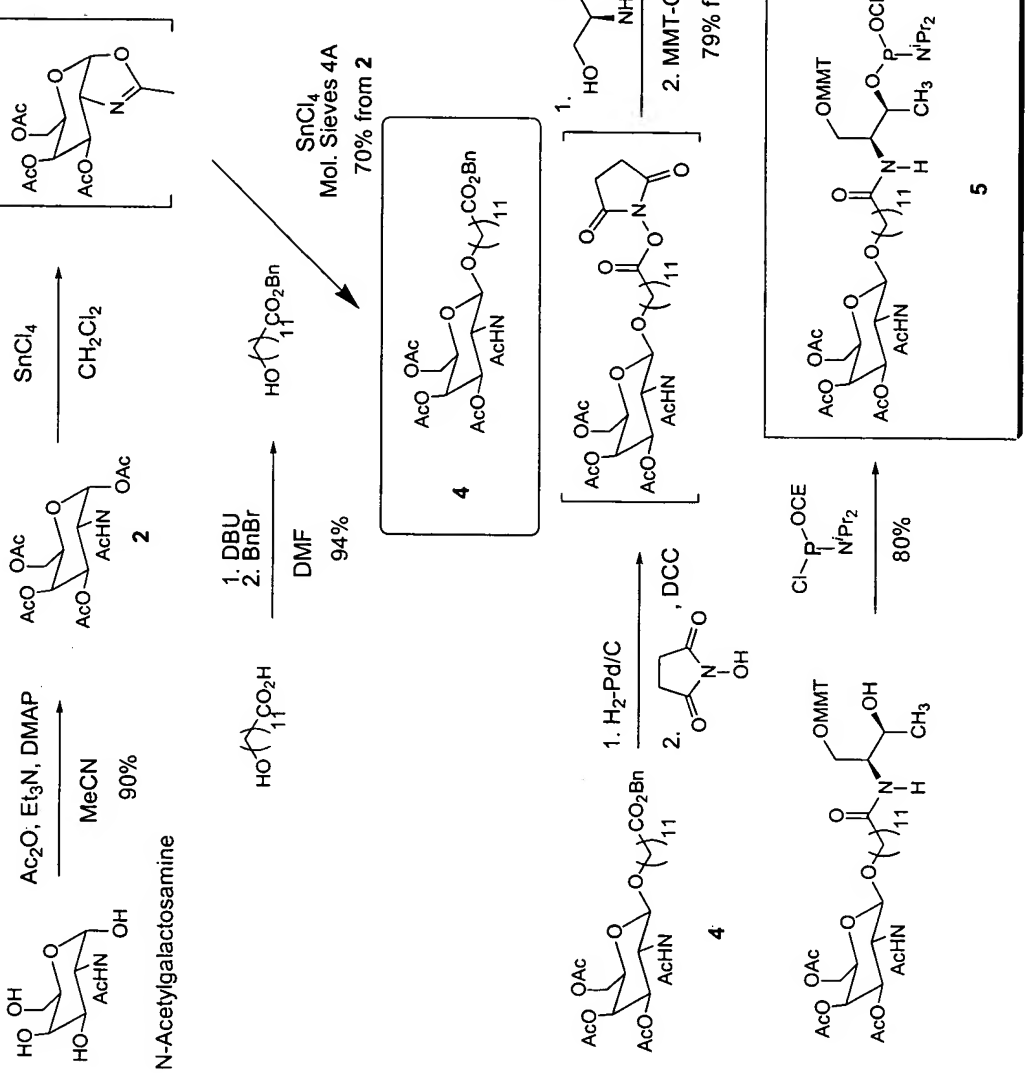


**Figure 70: Synthesis of "tri" Galactosamine phosphoramidite**

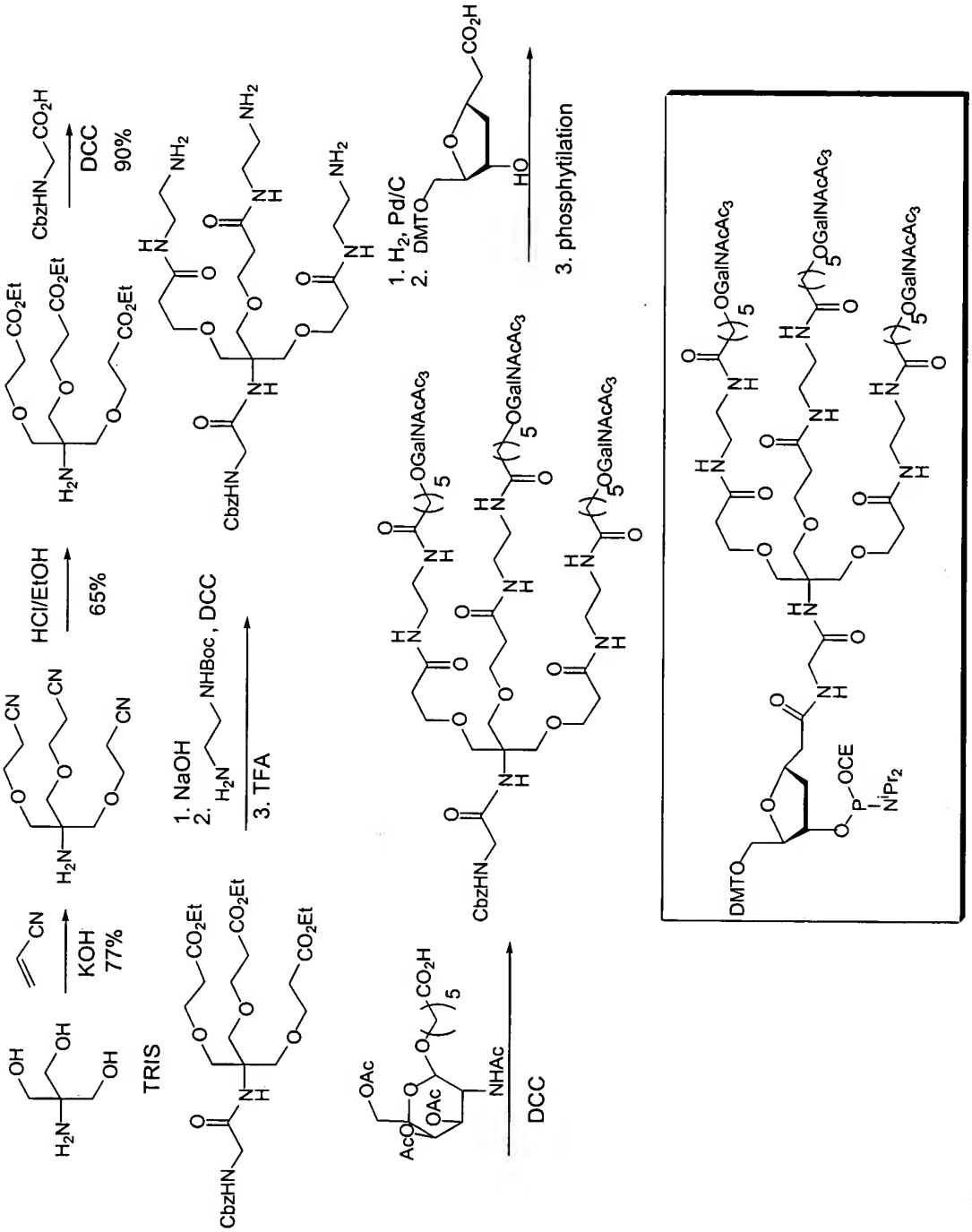
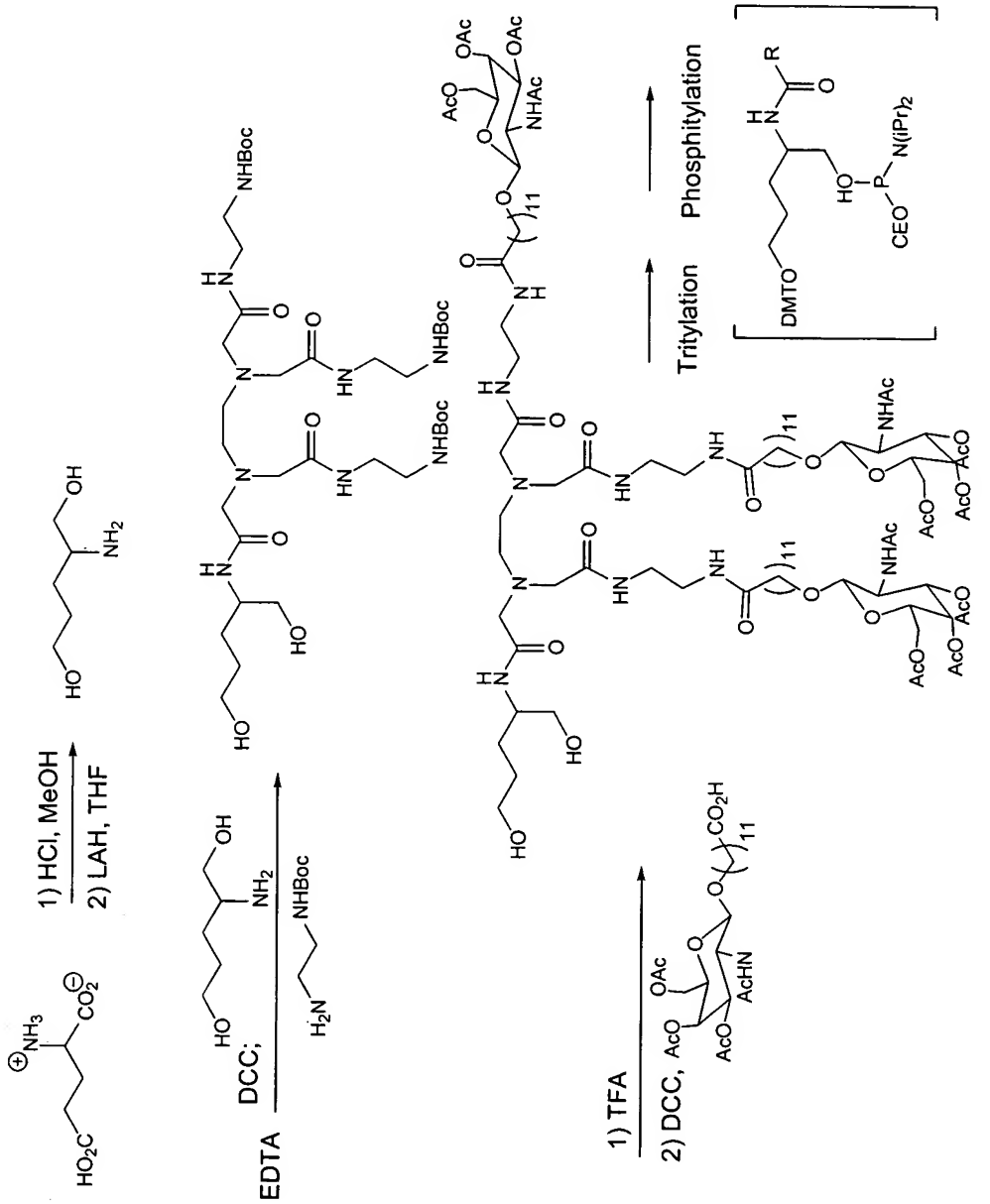


**Figure 71: Synthesis of another Tri-Galactosamine Conjugate**



## Figure 72: Alternate Synthesis of Tri-Galactosamine Conjugate

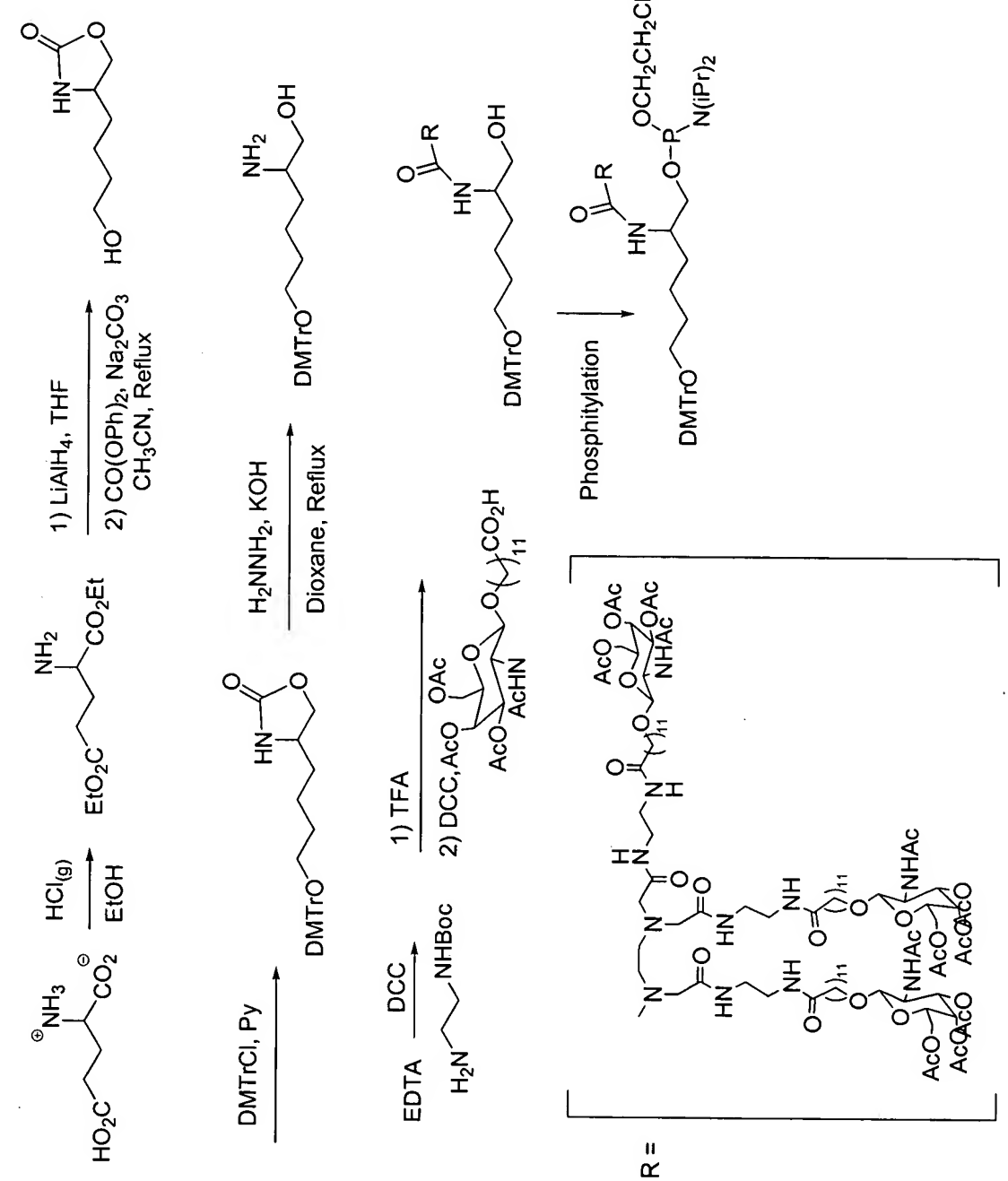
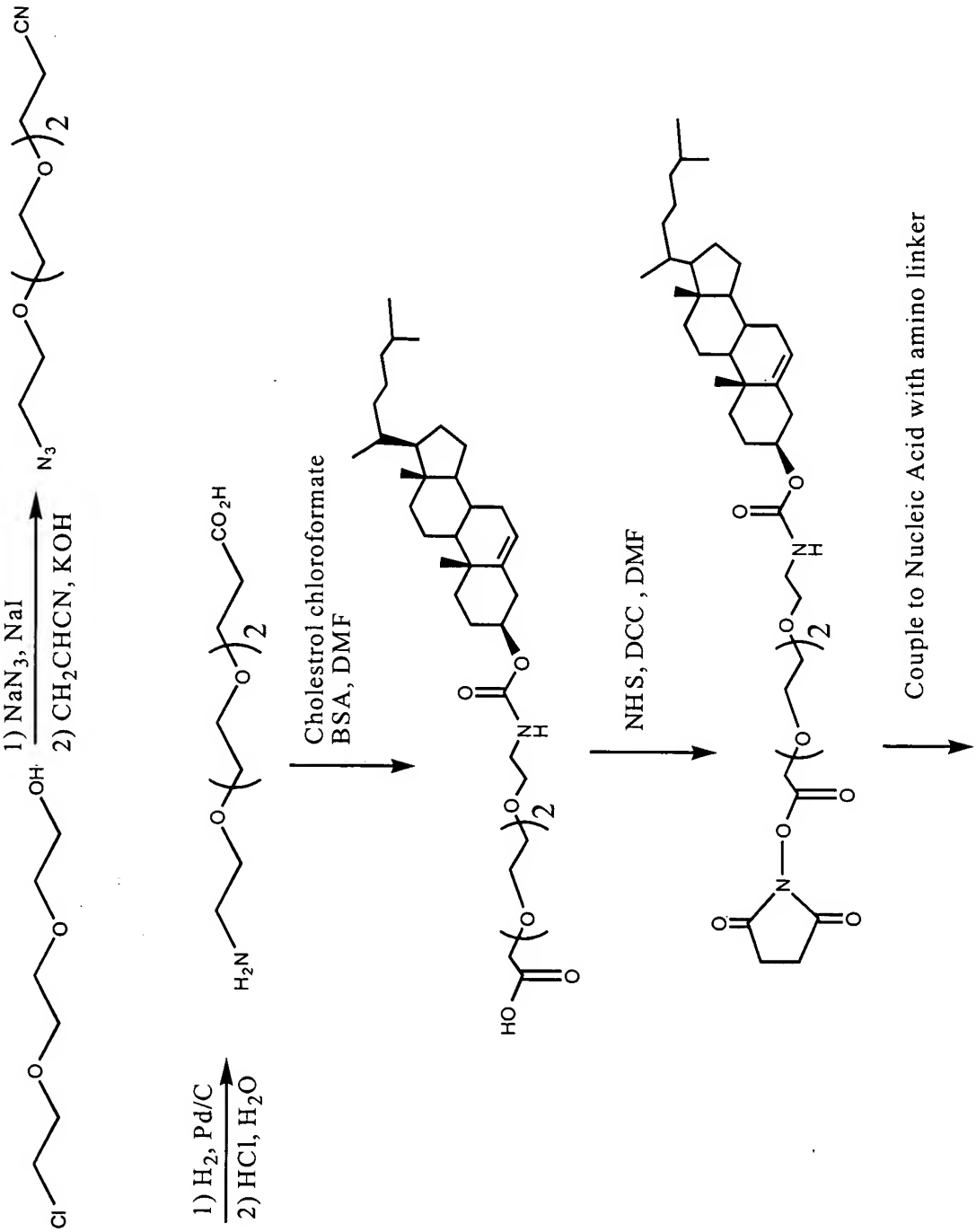
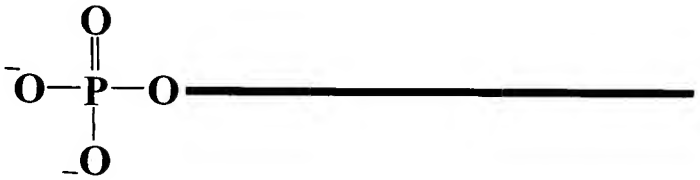


**Figure 73: Synthesis of NHS Cholesterol Conjugate**

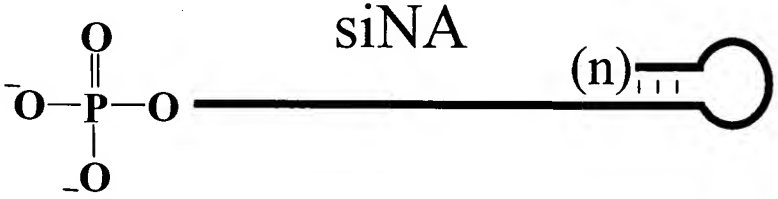


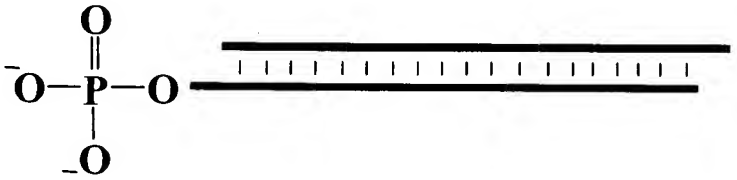
# *Figure 74: Phosphorylated siNA constructs*



Phosphates can be modified as described herein

Asymmetric hairpin siNA

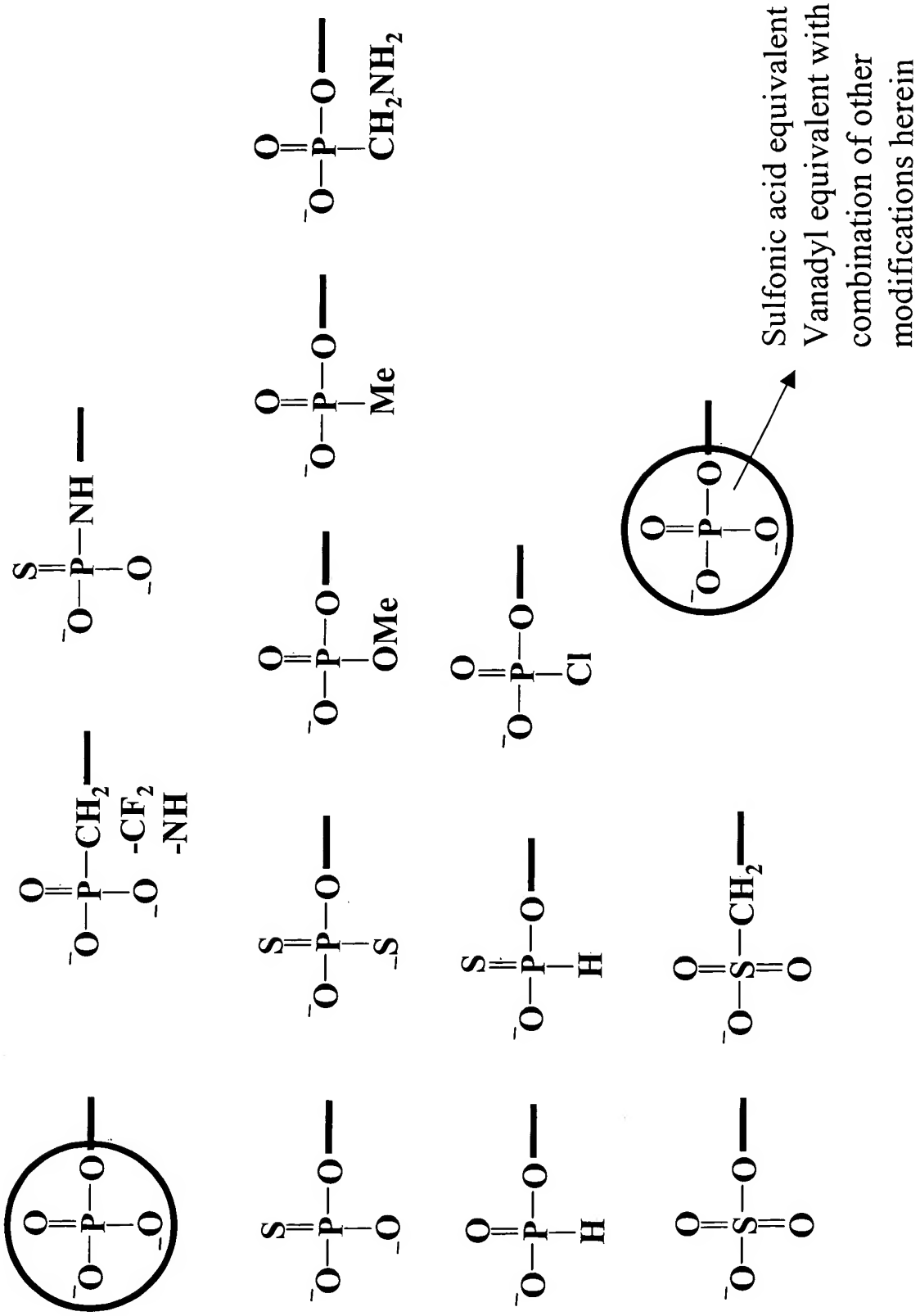


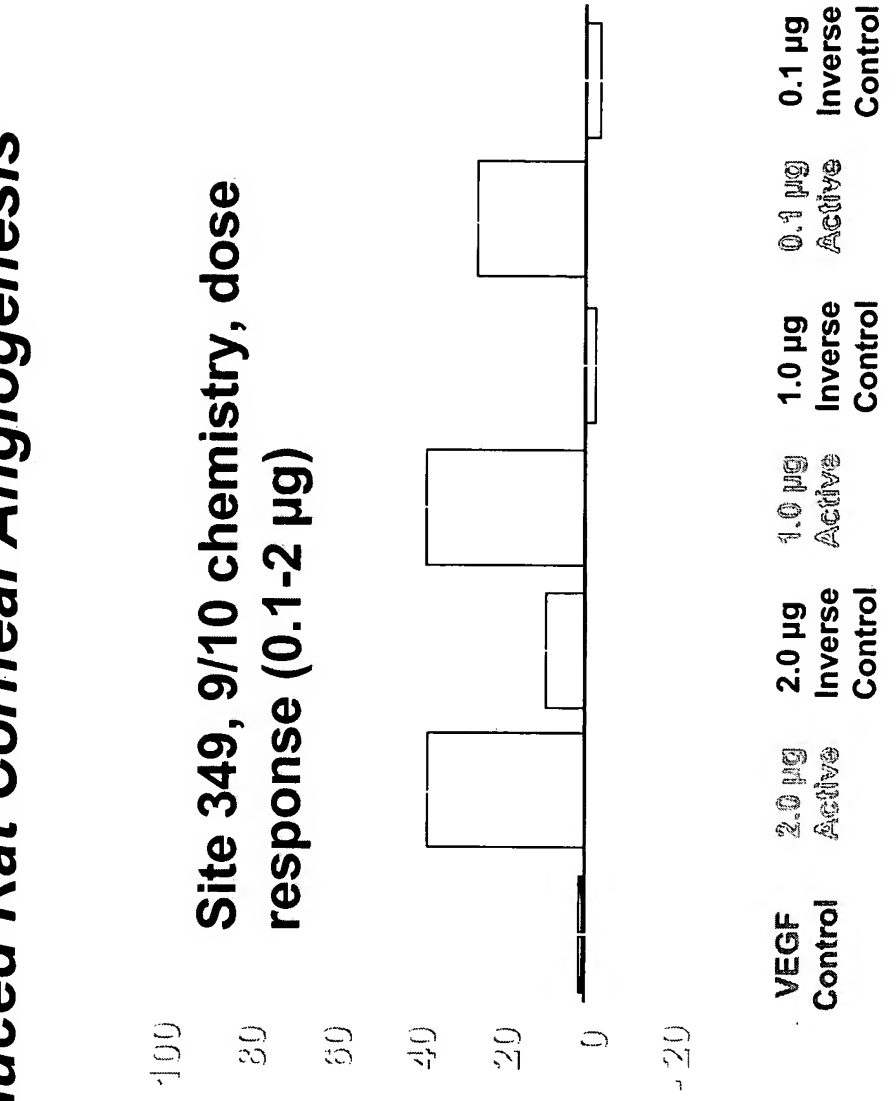
Asymmetric duplex siNA


(n) = number of base pairs (e.g. 3-18 bp)

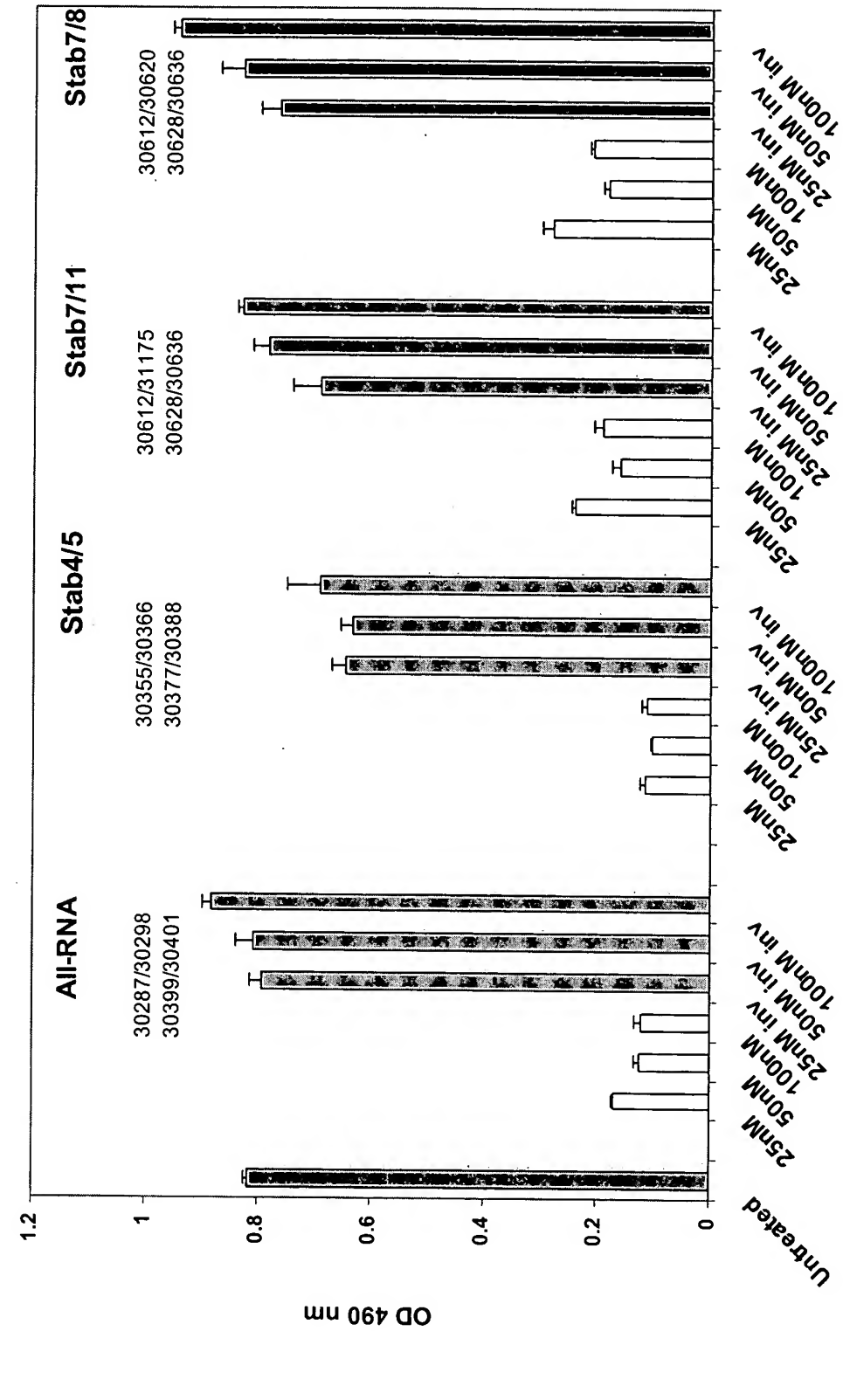
***Figure 75: 5'-phosphate modifications***



# *Figure 76: siNA Targeting VEGFR-1 Inhibits VEGF-Induced Rat Corneal Angiogenesis*



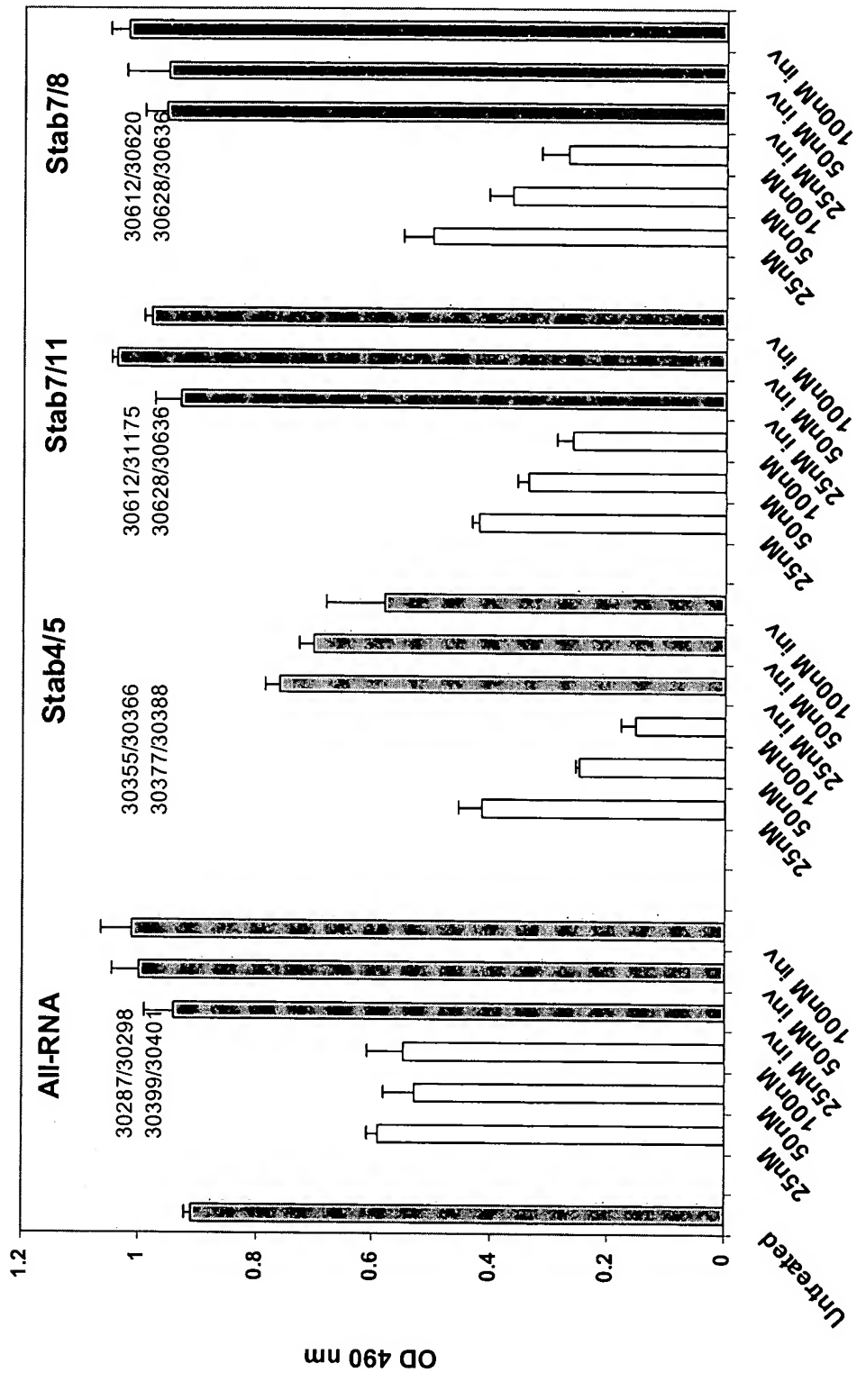
# Figure 77: Duration of Effect of Modified siNA Constructs



# Figure 77: Duration of Effect of Modified siNA Constructs

HBV siRNA Duration: Day 9

B



C

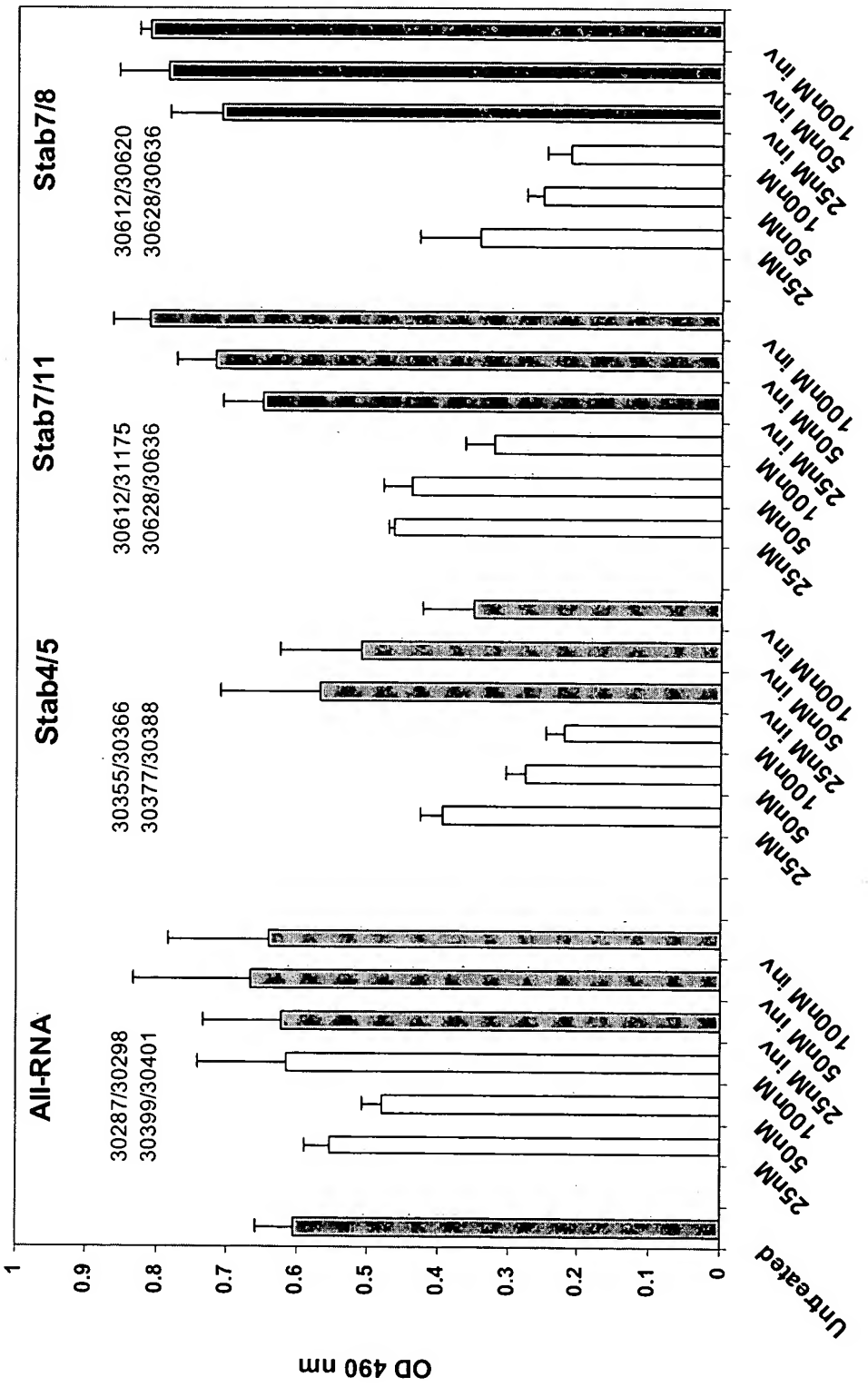
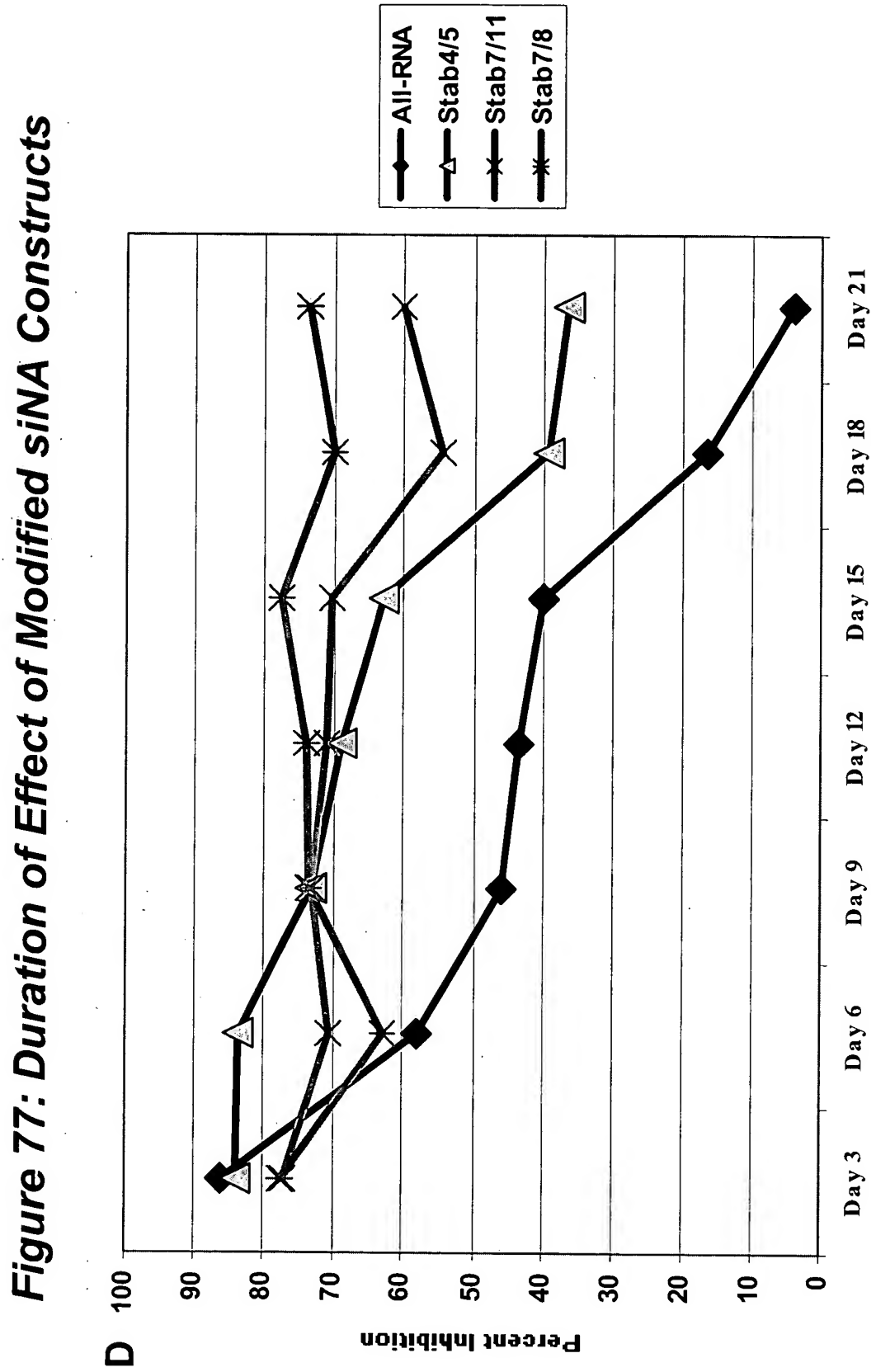


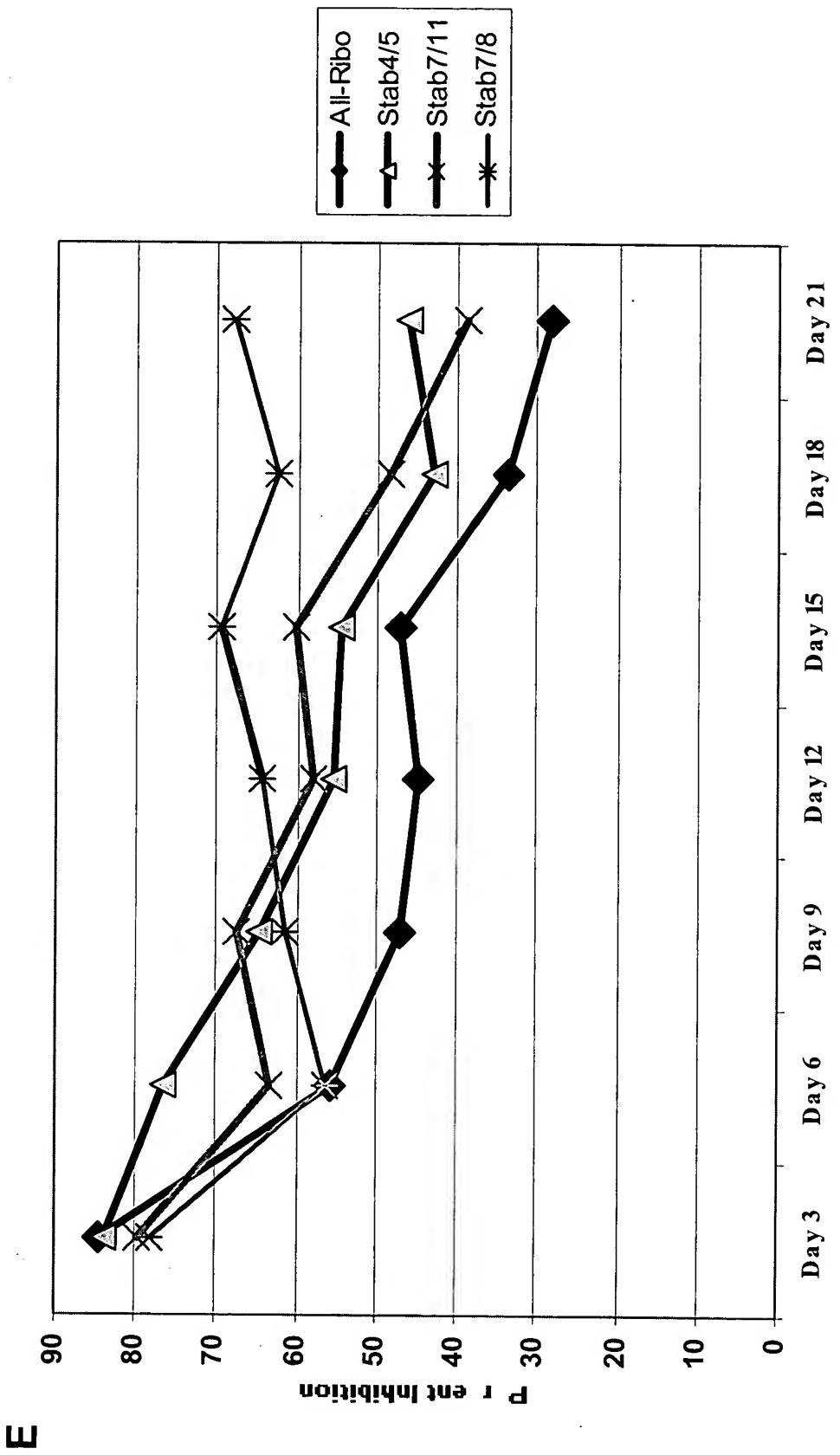

**Figure 77: Duration of Effect of Modified siNA Constructs**

HBV siRNA Duration: Day 21



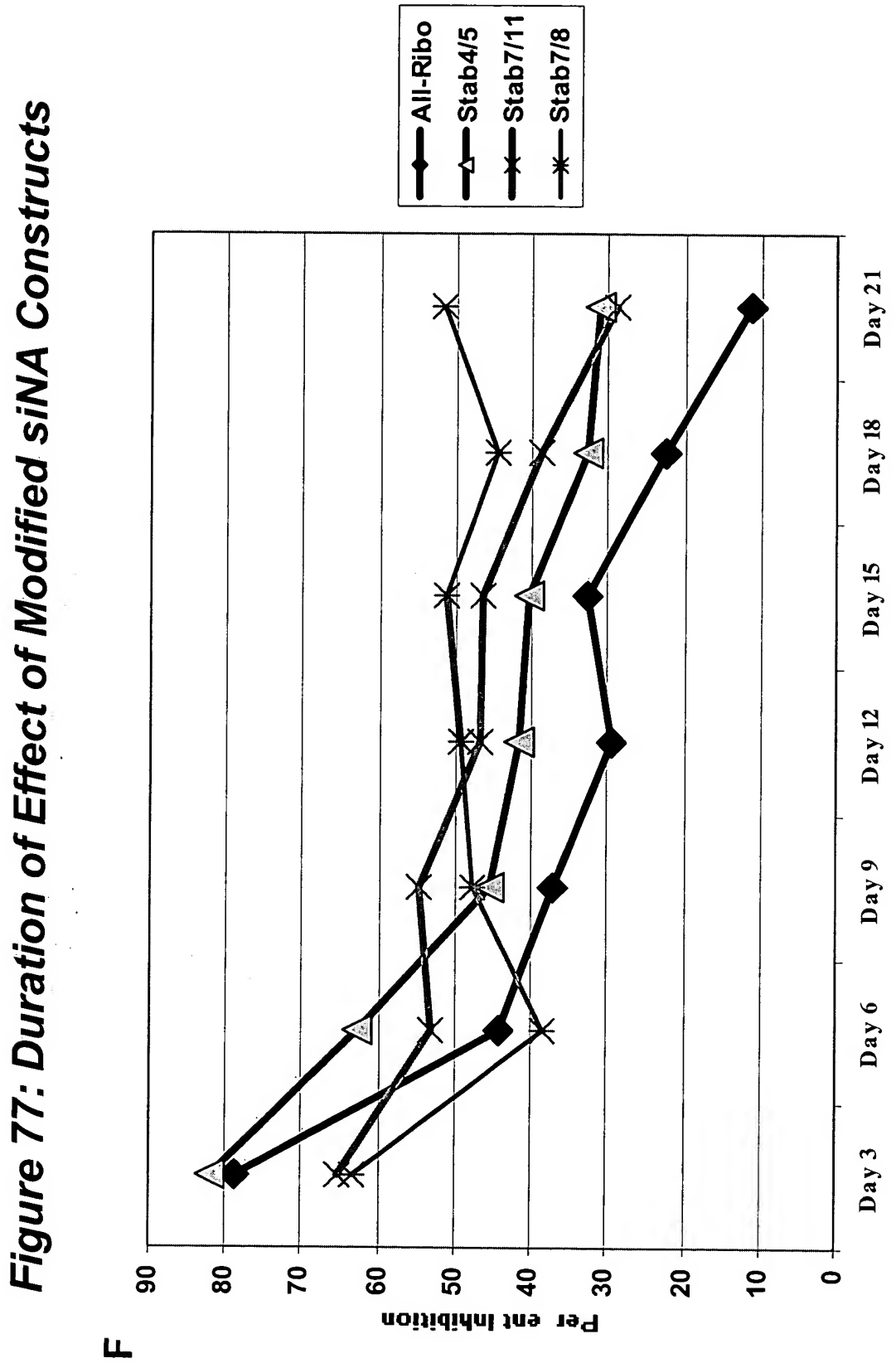

D

Figure 77: Duration of Effect of Modified siNA Constructs




E

**Figure 77: Duration of Effect of Modified siNA Constructs**



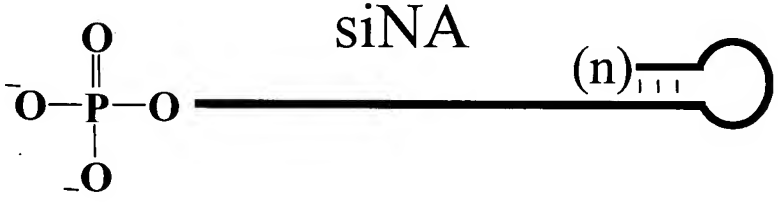

F

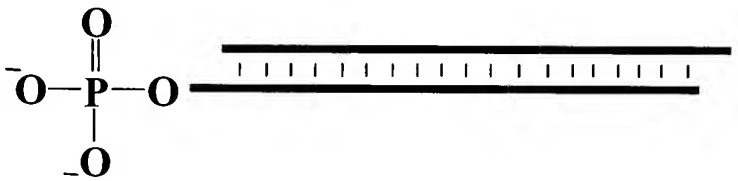
Figure 77: Duration of Effect of Modified siNA Constructs

# *Figure 78: Phosphorylated siNA constructs*

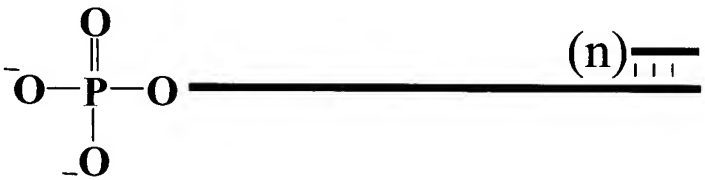
Phosphates can be modified as described herein

Asymmetric hairpin siNA



Asymmetric duplex siNA




(n) = number of base pairs (e.g. 3-18 bp)

# *Figure 79: 5'-phosphate modifications*

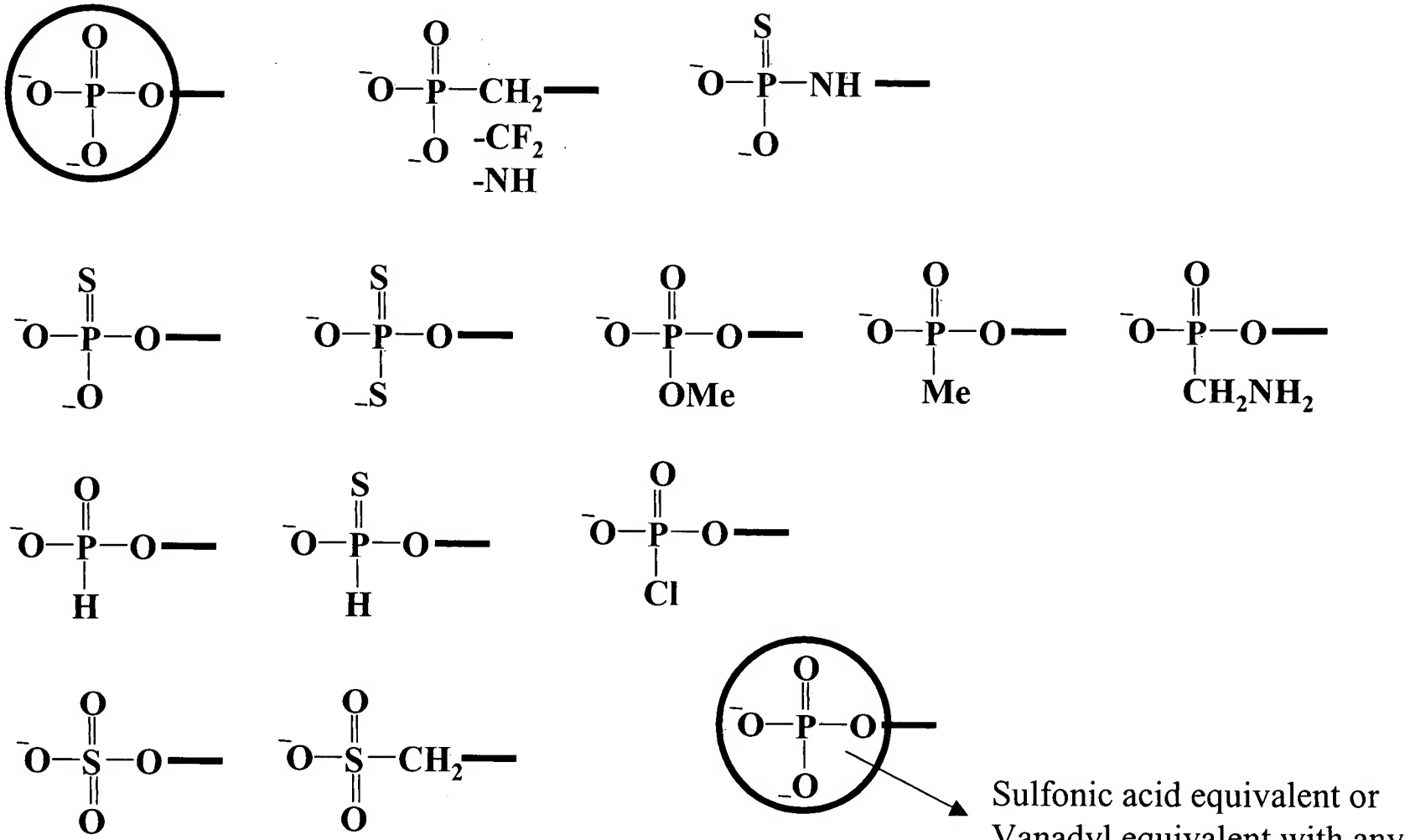


***Figure 80: Serum HBV DNA in Mice Treated with siNA Via HDI***

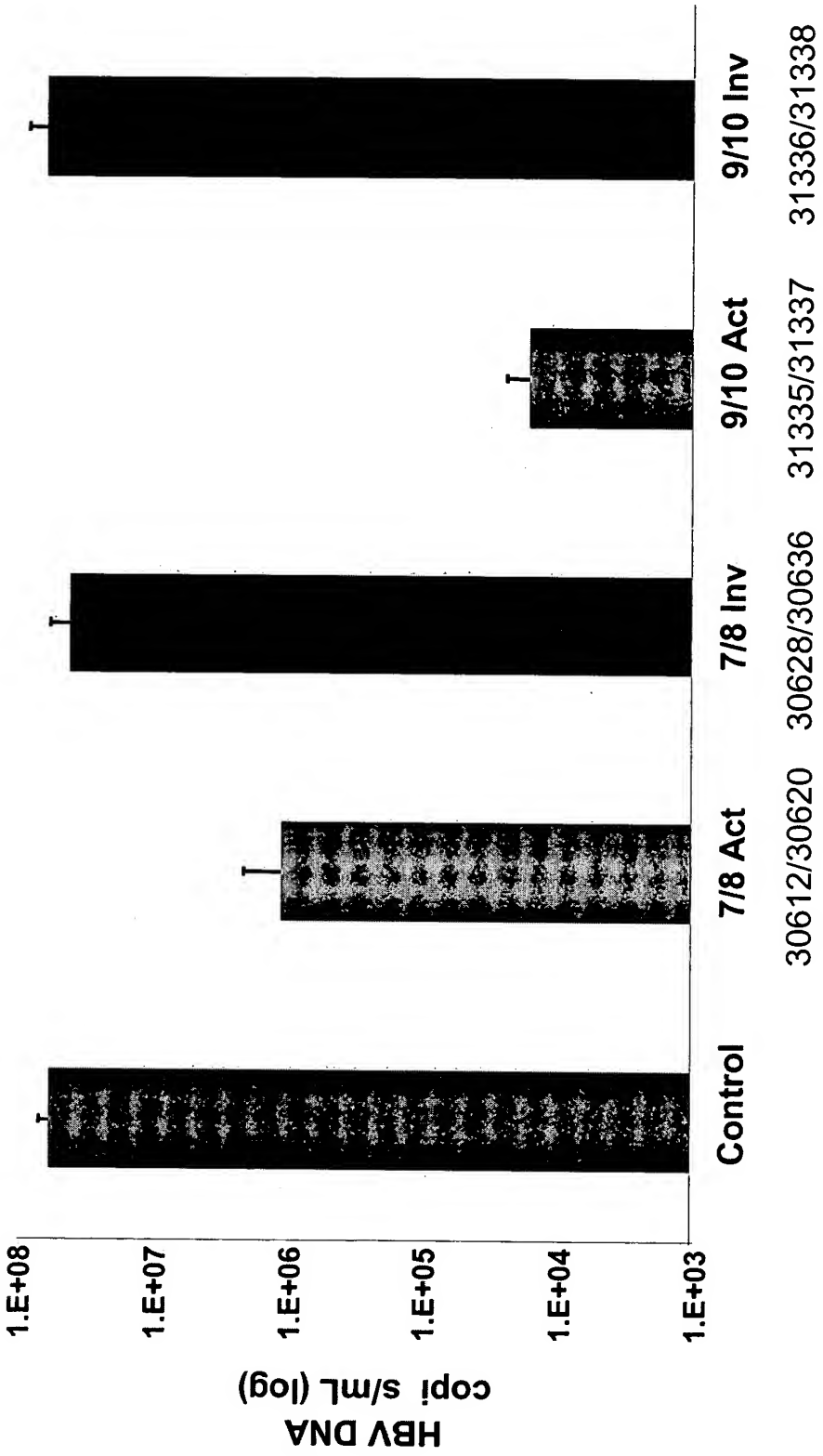
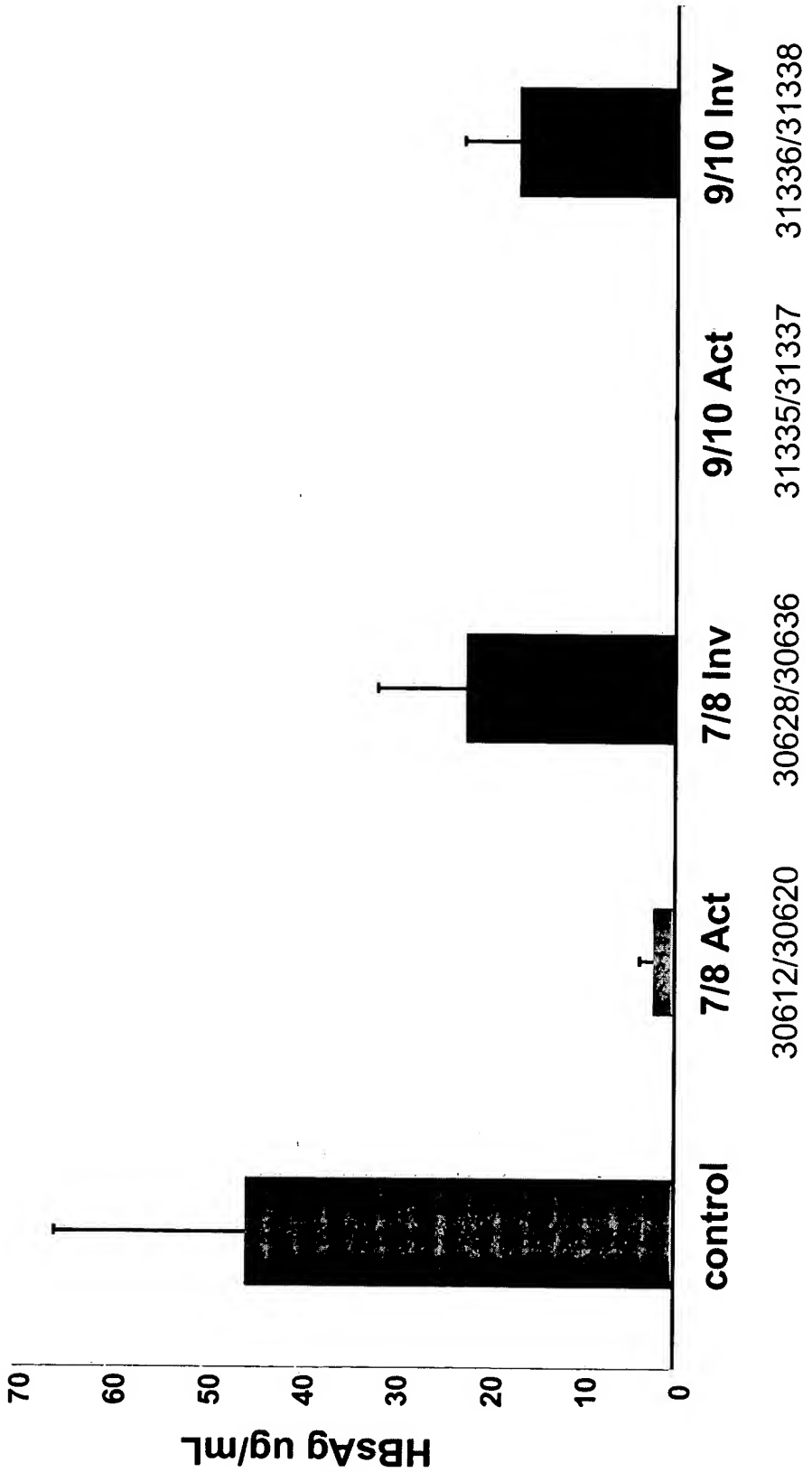


***Figure 81: Serum HBsAg in Mice Treated with siNA Via HDI***



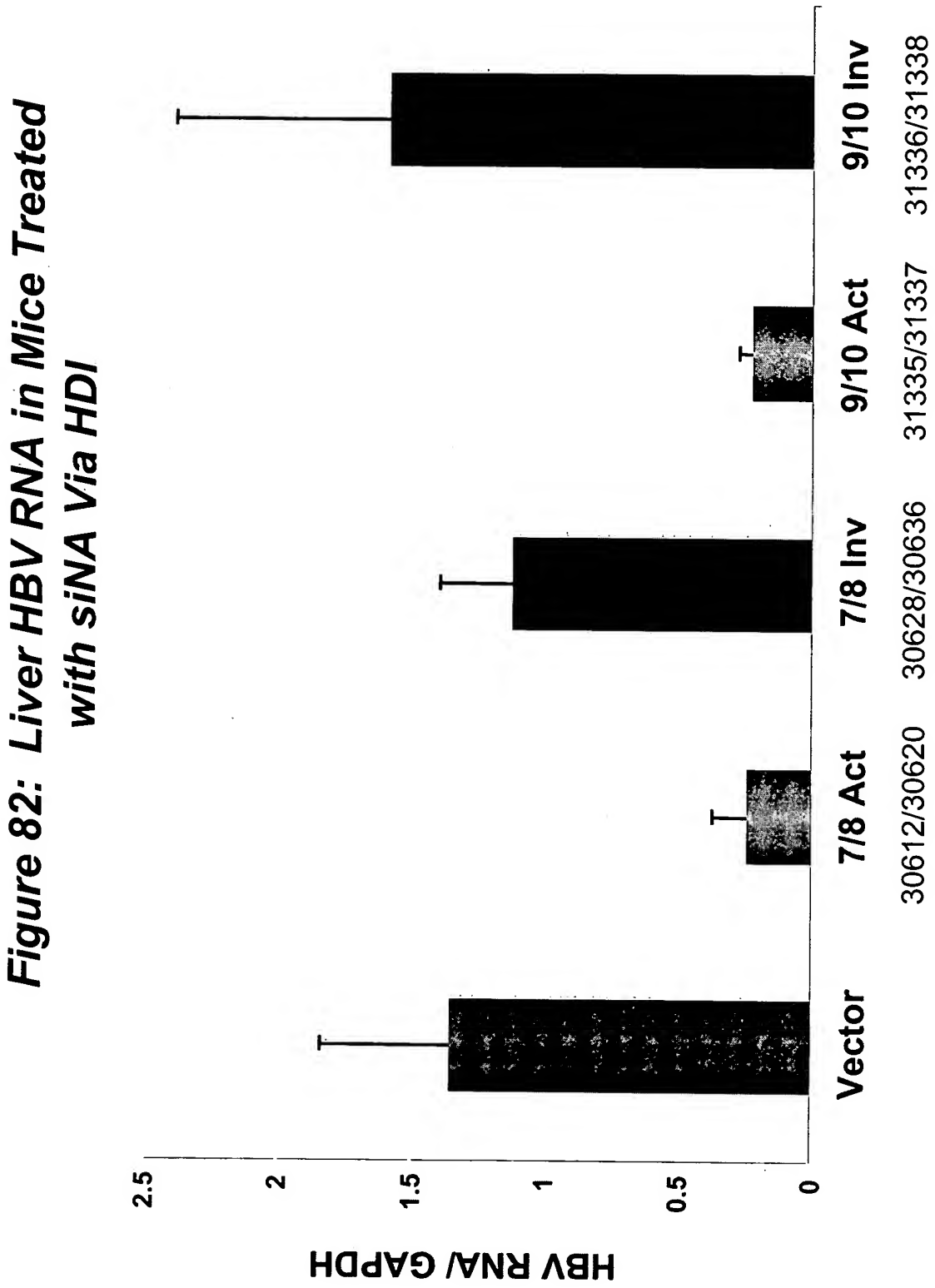
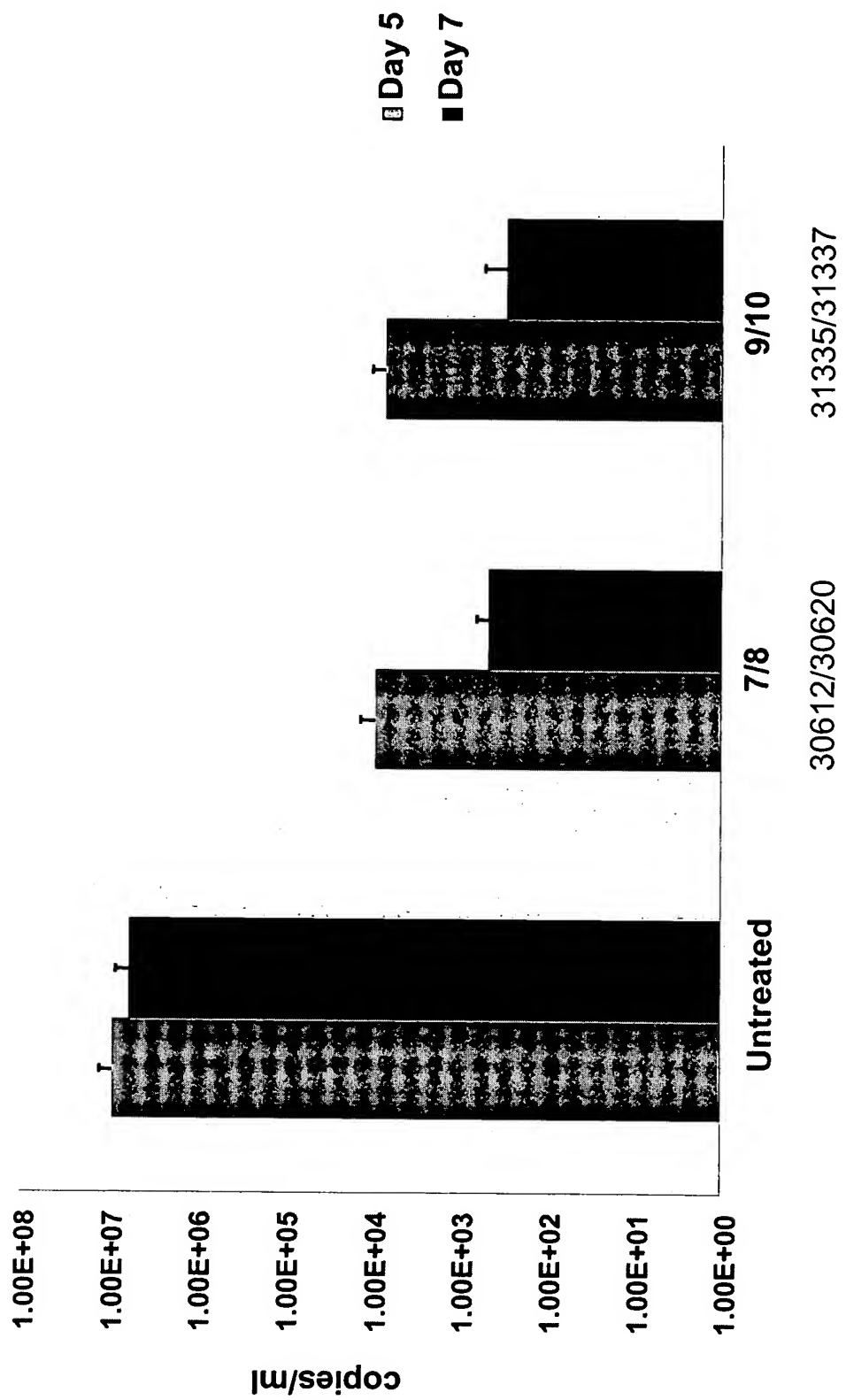



***Figure 82: Liver HBV RNA in Mice Treated with siNA Via HDI***

***Figure 83: Serum HBV DNA in Mice Treated with siNA Via HDI 5 and 7 days post treatment***



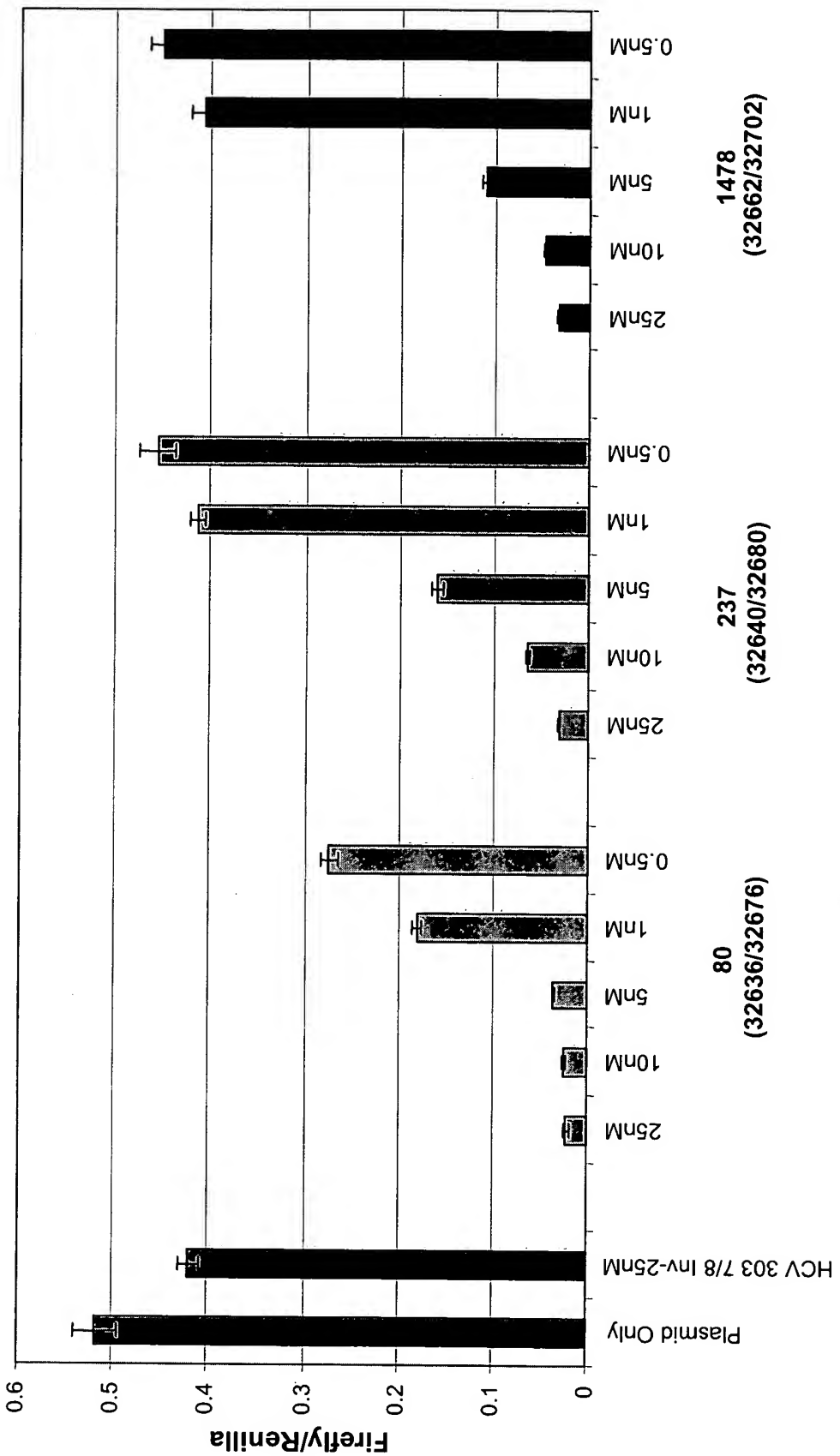



**Figure 84: Luciferase Dose Response of select active siNA constructs**

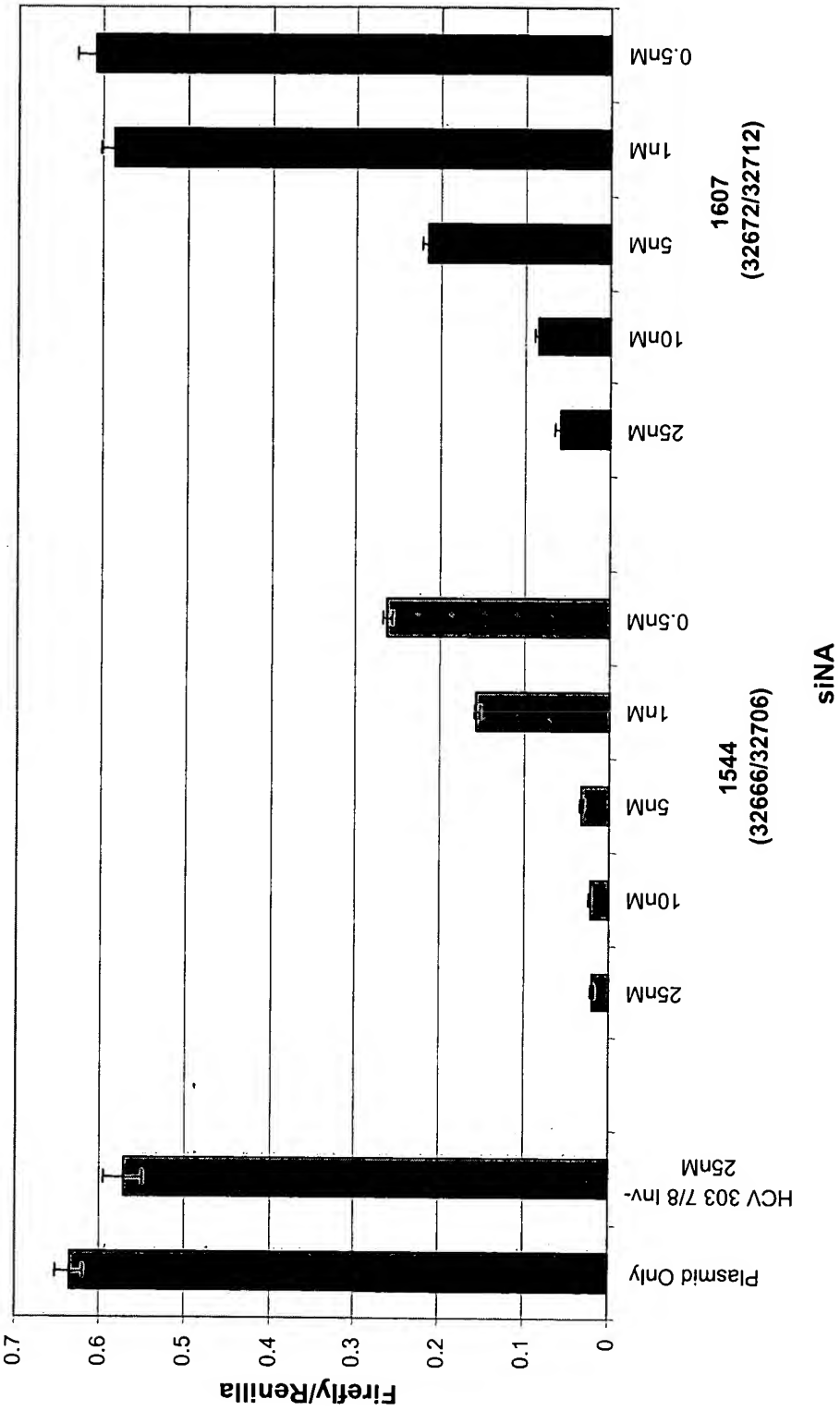



**Figure 85: Luciferase Dose Response of select active siNA constructs**

**Figure 86: Activity of Stab 7/8 Stabilized siNAs in HCV Replicon**

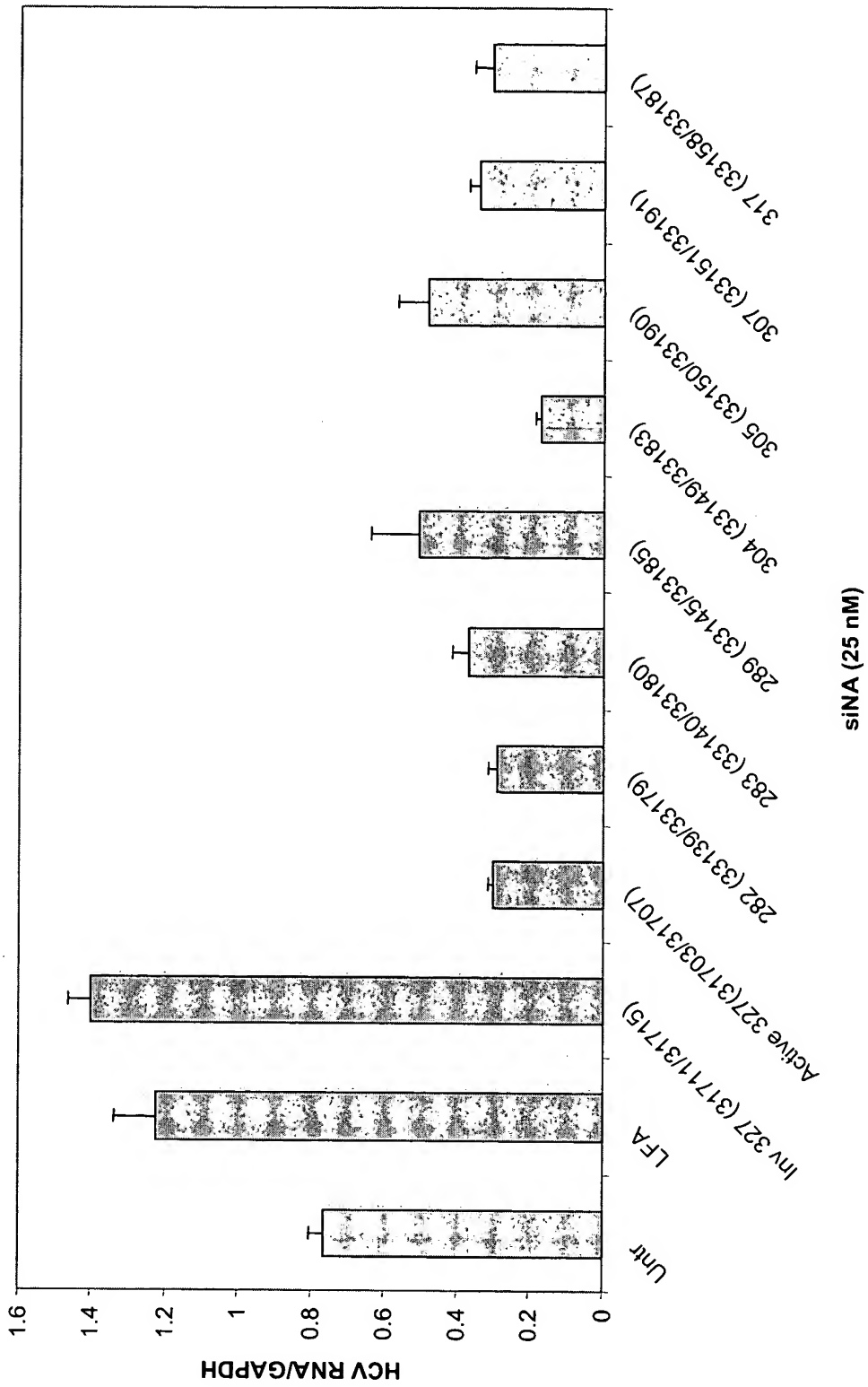


**Figure 87: Activity of Stabilized 7/8 siNAs Against HBV in HepG2 Cells**

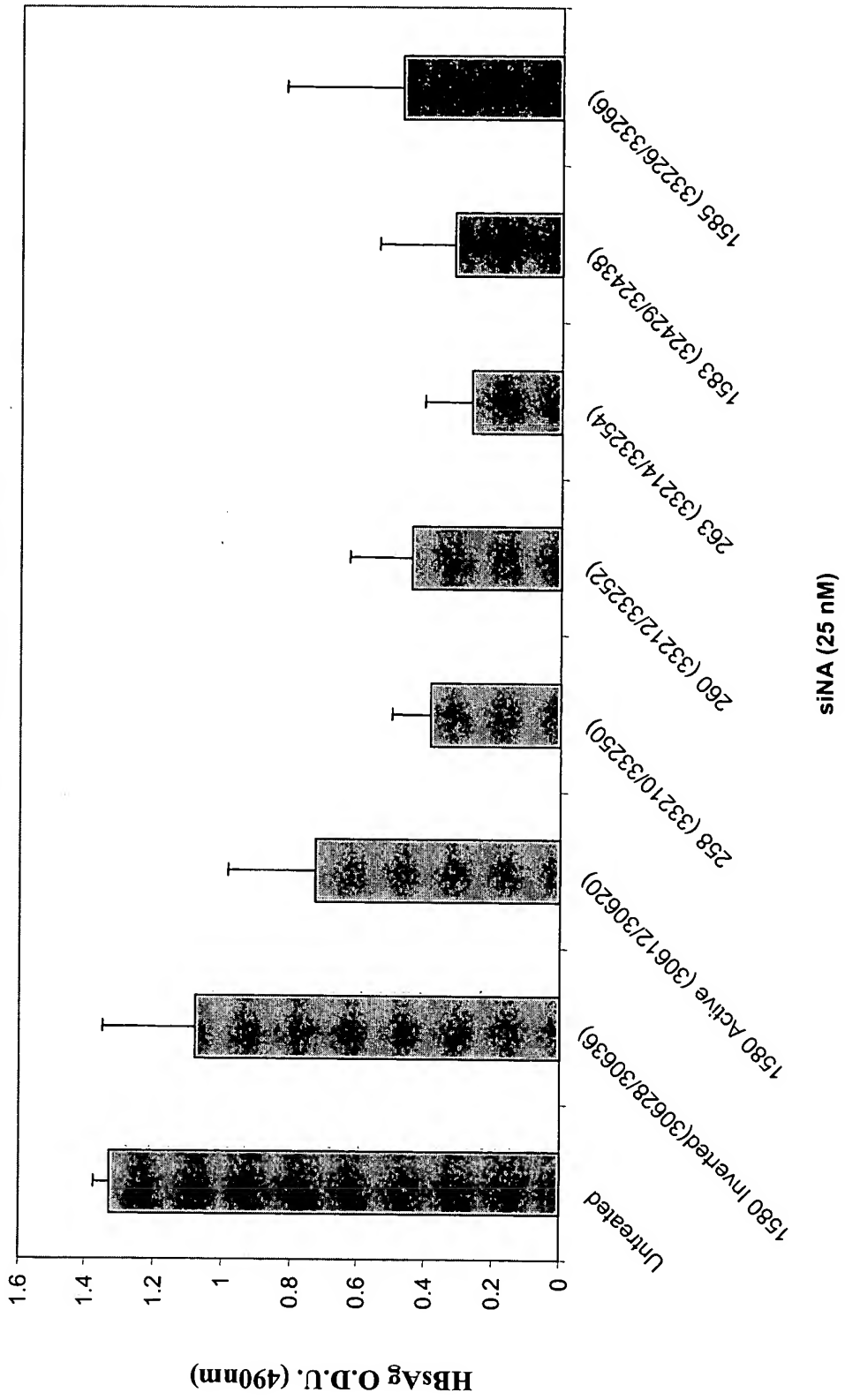


*Figure 88: HBV/siNA to site 1580 Combination Constructs*

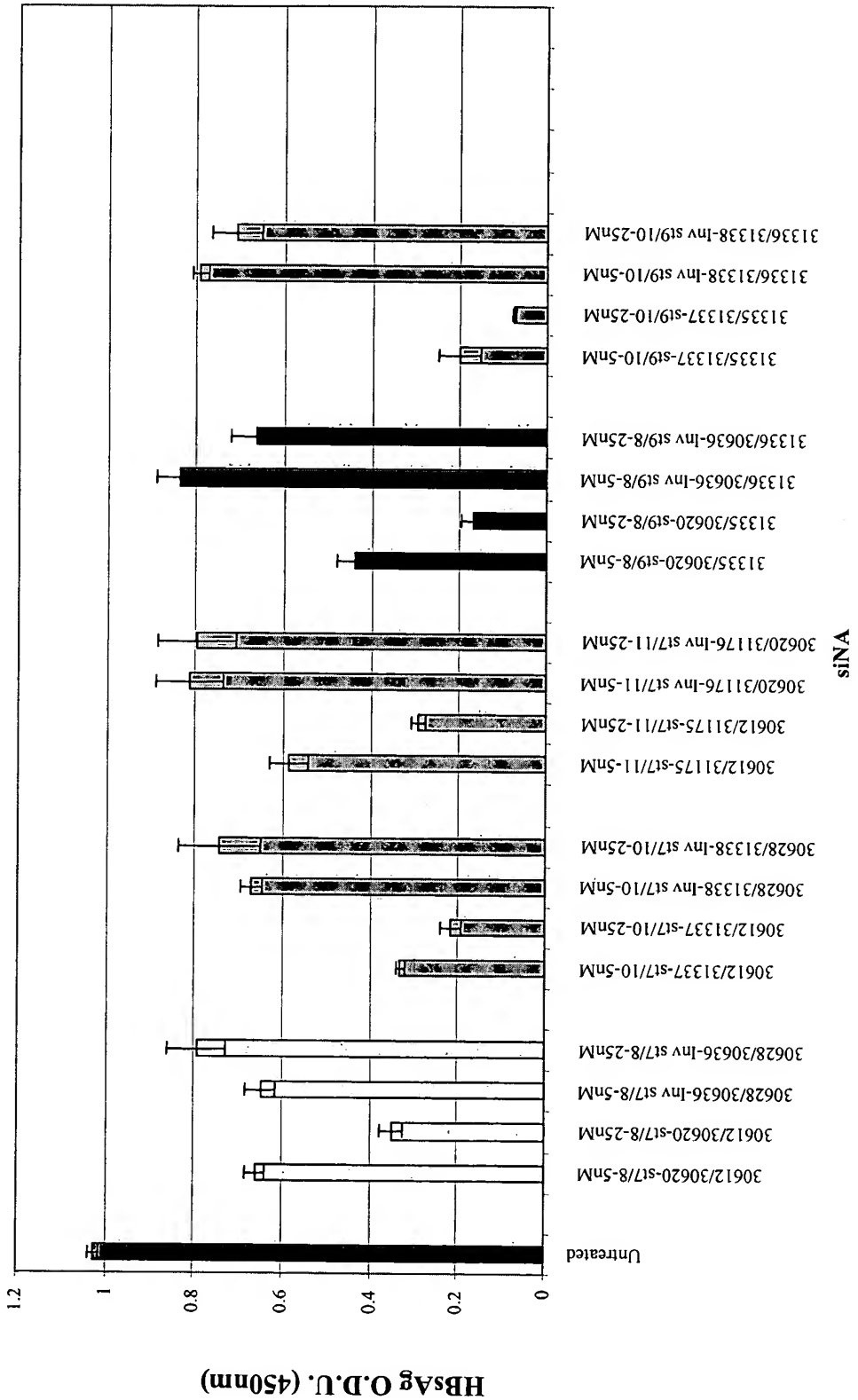
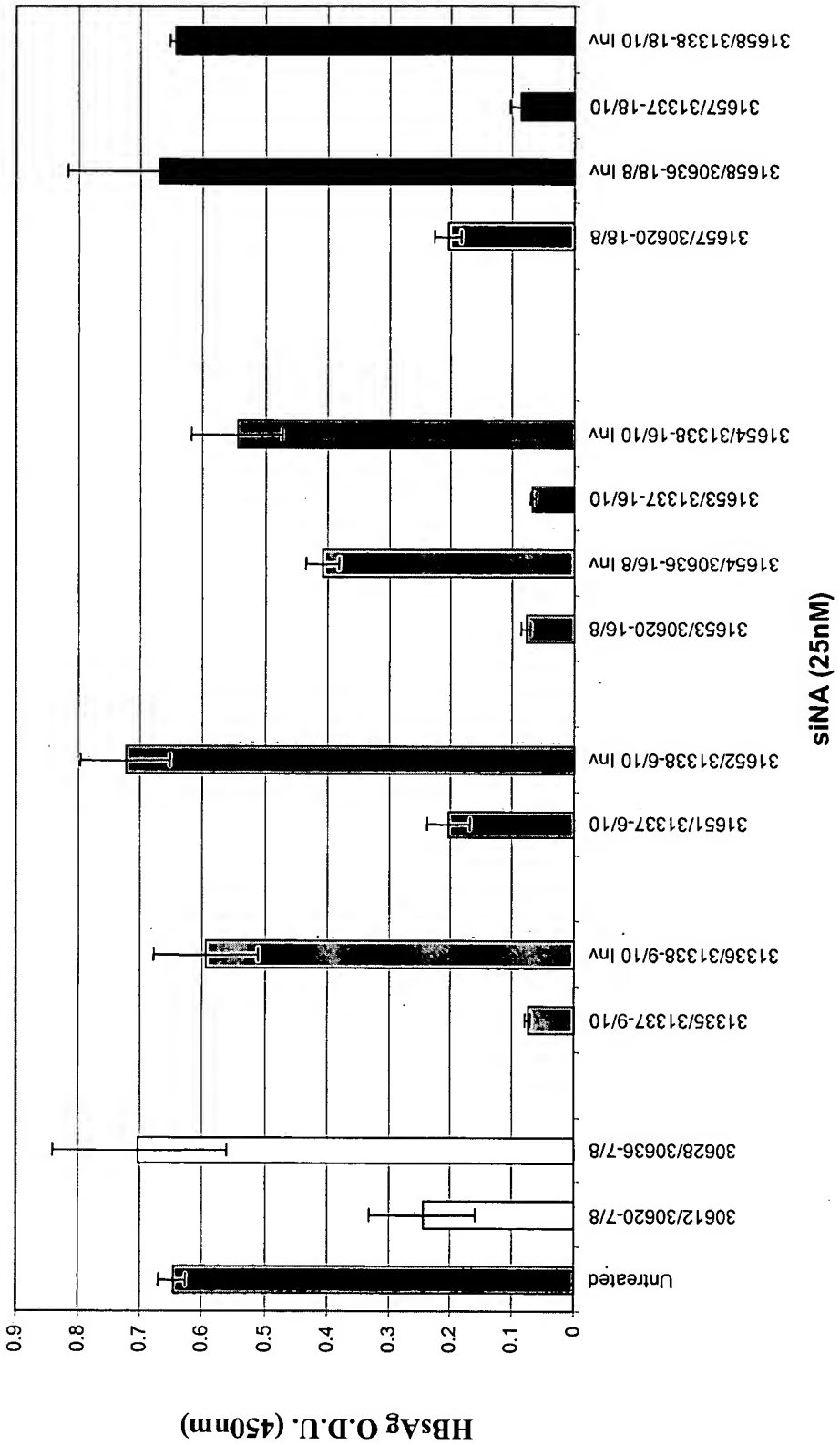


*Figure 89: HBV/siNA to site 1580 Combination Constructs*



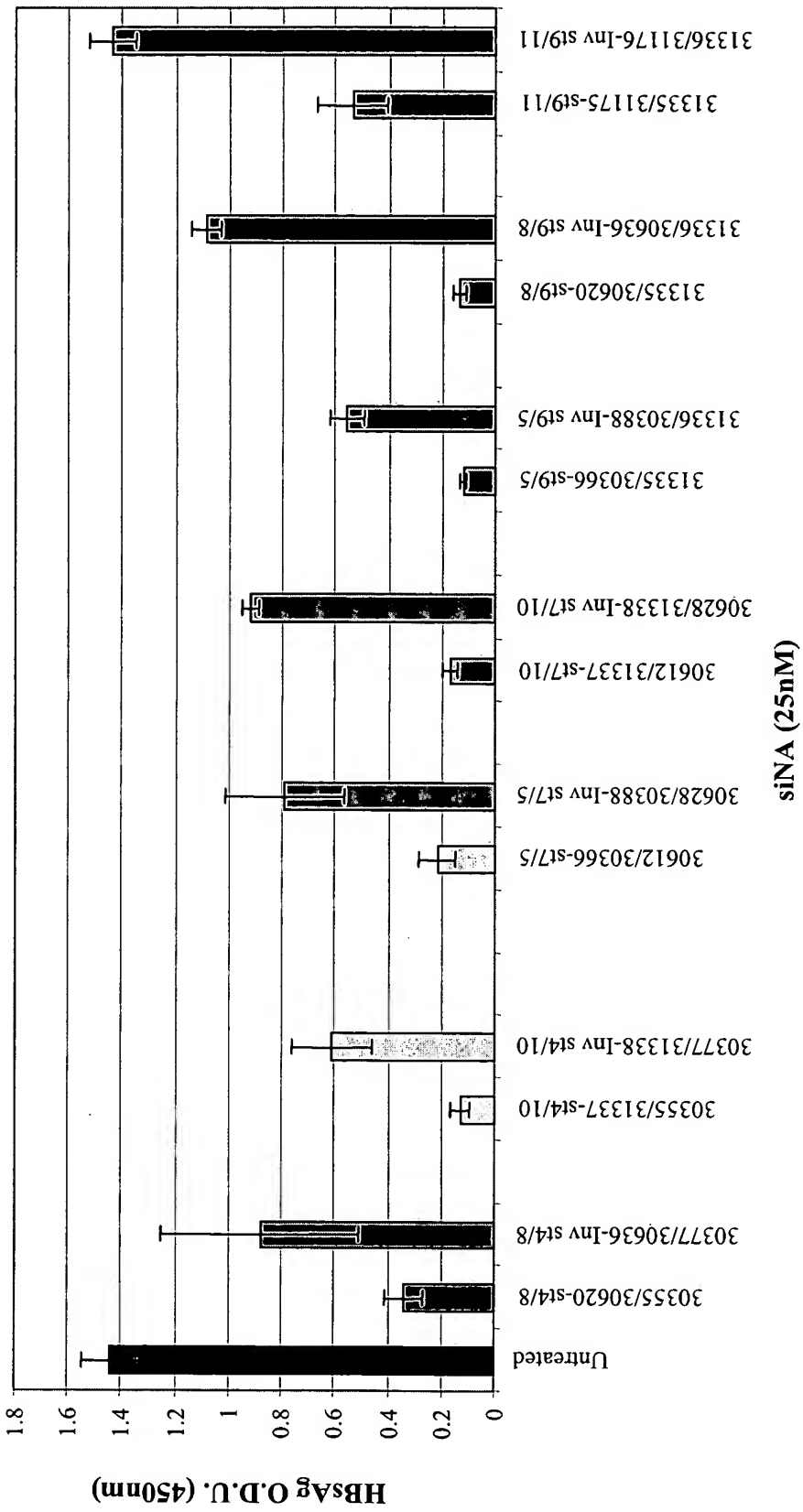



***Figure 90: HBV/siNA to site 1580 Combination Constructs***